INFLUENZA

AND OTHER VIRUS INFECTIONS OF THE RESPIRATORY TRACT

by

C. H. STUART-HARRIS
M.D., F.R.C.P.
Professor of Medicine, University of Sheffield

With a Foreword by

C. H. ANDREWES
M.D., F.R.C.P., F.R.S.
Deputy Director, National Institute for Medical Research



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FOREWORD

With the increasing success of antibiotics in bacterial infections, the virus diseases bulk ever larger as causes of human illnesses, some serious, others mere nuisances. Chief among these, at any rate in temperate climates, are the infections of the respiratory tract. At present they constitute a hotch-potch from which definite entities have to be picked out. Influenza A and B, and quite recently C, psittacosis and Q fever can be recognised as entities, though often only by the aid of laboratory tests. For most of the commoner respiratory infections treatment is purely symptomatic, and perhaps for that reason the busy practitioner does not worry too much about exact diagnosis, being content to use in borderline cases such non-committal terms as an '*influenza cold*'.

Knowledge about the diseases concerned is, however, steadily accumulating Practitioners and others will have so much of their time occupied in dealing with them that they will do well to make themselves aware of what is known and what is still vague and nebulous Professor Stuart-Harris's book is, for such a purpose, 'just what the doctor ordered'—or should order. He is better qualified than anyone else in Britain to write a book such as this, for there are few if any clinicians who know so much of the laboratory side of the work, and certainly no laboratory worker knows the clinical side so well. Most attention is naturally paid to influenza both because of its importance as a potential killer and because of the accumulation of knowledge about it by concerted clinical, epidemiological and laboratory studies Chapter 5, on laboratory diagnosis, is not 'everybody's meat', but there will be many who will be glad to refer to the detailed information it contains

As a former colleague of Professor Stuart-Harris, I am glad to record my satisfaction at the appearance of this book, which will be of value to public health workers, clinical pathologists and advanced students, but especially, I feel, to the alert 'G P.'.

C H. ANDREWES

ACKNOWLEDGEMENTS

THE research work quoted in this book could not have been carried out without the active help and co-operation of many doctors both in and outside hospital practice. I wish particularly to thank those members of the staff of the University Department of Medicine who have, during the past six years, given me much vital assistance. Particularly is this so in regard to the work of Miss J. C. Appleby, Dr. Margaret R. Davies-Jones, Miss Z. Franks, Dr. P. W. W. Gifford, Dr Alick Isaacs, Dr. Joan Laird, Dr. Margaret H. Miller and Dr. David A J Tyrrell. I have quoted freely from the results of pneumoccocus typing reported by Miss M Pownall of the Public Health Laboratory Service, Sheffield, and of staphylococcus typing by Dr. R. E. O. Williams of the Central Public Health Reference Laboratory, Colindale.

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Dr. Llywelyn Roberts, Medical Officer of Health of the City of Sheffield, has kindly allowed me to quote the statistics relating to the incidence and fatality of pneumonia in the city.

I should like to thank Dr Alick Isaacs, of the World Influenza Centre, London, and Dr W. N. Pickles of Aysgarth, Wensleydale, for much help in the preparation of the manuscript and Miss P. M. Townend for invaluable clerical assistance

The terramycin used on patients referred to in this book was a gift kindly supplied by Dr Gladys Hobby, Chas. Pfizer & Company, Inc , New York

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CHAPTER I

CLASSIFICATION OF THE VIRUS INFECTIONS OF THE RESPIRATORY TRACT

THE respiratory tract in man has a restricted response to attack by the various bacteria and viruses capable of causing inflammation of its epithelium. Whatever may be the exciting cause, an inflamed nasal mucosa can complain only by being hyper-irritable, swollen, or by exuding a surface secretion of mucus and leucocytes. The resultant symptoms of sneezing, obstruction to the passage of air and of catarrh constitute the range of response of the nose to acute inflammation, whether the cause be a common cold, or an influenza, or a grass pollen. Similarly, the pharynx chiefly complains by feeling sore, or dry, or tickling, and the voice loses its tone or becomes frankly hoarse because of œdema and hyperæmia of the vocal cords The trachea and bronchi complain by causing cough, and particularly a productive cough, and also frequently by a sense of substernal soreness or tightness This is as characteristic of the response of an acutely inflamed tracheal and bronchial mucosa as is the pain on swallowing felt from an inflamed pharynx. It is small wonder that the physician who seeks diagnostic accuracy is driven to use anatomical words such as rhinitis, pharyngitis, laryngitis, tracheitis and bronchitis for the various acute infections of the respiratory tract. Unfortunately, however, such terms are not accurate as descriptions and give no hint of ætiology

Even with the present imperfect knowledge of the viruses of the respiratory tract, it is abundantly clear that the same agent can produce an illness characterised predominantly by rhinitis or pharyngitis, or by laryngitis, or a tracheo-bronchitis. Moreover, it is probable, though not yet certain, that different viruses actually produce closely similar clinical pictures This is apparently due to the fact that the virus infections of the respiratory tract are frequently local infections involving only the mucosa There is no systemic spread of virus, there are no rashes. Contrast influenza with measles or small-pox, in both of which the virus lesions in the respiratory tract furnish only an incidental accompaniment of the general systemic infection, and it is obvious that influenza is an infinitely more difficult condition to diagnose clinically.

The explanation of the clinical obscurity of the various virus

infections of the respiratory tract lies therefore partly in the character of the virus attack and partly in the restricted range in clinical response of the air-passages. Small wonder that it was not until the laboratory came to the rescue that it became possible to begin to disentangle the diverse disorders hidden in the general scrap-heap of clinical influenza, nasopharyngeal catarrh and the common cold. The present phase is still that of delineation first of one and then of another of the clinical syndromes to which ætiological agents can be ascribed. Inevitably a large, ill-defined conglomeration or rubbish-heap remains, amongst which many entirely different conditions are hidden. This is the hard core of the problem of

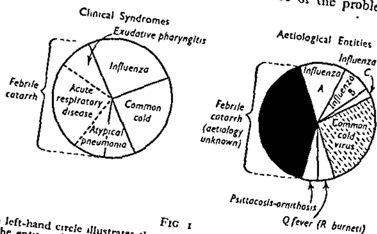


FIG 1

The left-hand circle illustrates the various clinical syndromes, and that on the right the entities thus far delineated and shown to be due to the various named virus or rickettsial agents

acute undifferentiated respiratory disease after separation of the clinical territories of epidemic influenza, of the common cold, of atypical pneumonia and of bacterial infections such as strep- tonsillitis In each of these defin... concern...

c

a

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Thus including the territory which is unclaimed as yet in terms of ætiological agents, we have four chief clinical syndromes which together furnish the group of virus infections of the respiratory tract in man These are influenza due to the various influenza

viruses, the common cold due to the cold virus, atypical pneumonia due to known virus and rickettsial agents and acute undifferentiated respiratory disease or febrile catarrh. The last-named includes exudative pharyngitis, acute respiratory disease (A R.D.) and primary atypical pneumonia of uncertain ætiology. The diagram (Fig. 1) may serve to illustrate this classification, by comparison of the field of the various clinical syndromes on the left with that built up so far from known causative agents and shown to the right.

History of the delineation of clinical syndromes

The manner of delineation of these various entities belongs to contemporary and recent history. An account of it may serve to clarify the meaning of what has been written above. The first strains of influenza virus were recovered in London by Smith, Andrewes and Laidlaw (1933) from gargLings of patients at the close of one of the major epidemics of influenza in Great Britain. The clinical attacks during the outbreak were clear-cut, sharp illnesses with greater emphasis upon general or constitutional symptoms, such as headache, malaise and muscular aching, than upon the respiratory tract. The virus was transmitted to the ferret by intranasal inoculation with human garglings, and thence from infected ferrets to mice. A close resemblance to the virus of swine influenza discovered by Shope in 1931 was soon apparent. This virus was also pathogenic for the ferret and mouse, and some degree of cross-immunity was demonstrated between the two viruses in the ferret. Unlike swine influenza, which is a simultaneous virus and bacterial infection with the hæmophilus bacterium of pigs—*Hæmophilus influenzæ suis*—no immediate relationship was discerned between the human influenza virus and any nasopharyngeal bacterial species. There was, however, doubt concerning the pathogenic properties of the human virus until the discovery was confirmed and until accidental human infection with the virus had occurred in the laboratory. Francis (1934) confirmed the discovery of the ferret-pathogenic virus and showed that patients with influenza developed neutralizing antibodies for the virus in their serum during recovery from the disease. In 1936 a laboratory infection occurred as a result of an infected ferret's sneeze which indicated

influenza and from whose throats strains of virus were recovered. And virus strains analogous to the original W.S. strain were recovered from influenza epidemics in countries all over the world.

The next step was the discovery that some outbreaks of clinical influenza did not yield a ferret-pathogenic virus. This first came about in 1935, when two clinically similar localised outbreaks of influenza in Army units were investigated by the London workers. The outbreak in Kent readily yielded the familiar ferret-pathogenic virus; that at Woolwich did not. Further studies in Britain and the U.S.A. between 1935 and 1939 confirmed that virus was readily recovered during spreading influenza epidemics, but that localised outbreaks often failed to yield any evidence of infection by the virus. Workers in Britain in 1937 attempted to build up clinical criteria for separation of the influenza virus infection from the respiratory outbreaks which did not yield virus and which were called 'febrile catarrhs' (Stuart-Harris, Andrewes and Smith, 1938). Many of the outbreaks of febrile catarrh occurred in military garrisons, and during the second world war American workers also encountered and studied similar conditions, particularly in recruits. They used the alternative title of acute respiratory disease (A.R.D.), but found it difficult to build up sound clinical criteria distinguishing A.R.D. from influenza virus infection (Commission on Acute Respiratory Diseases, 1948).

Meanwhile, in 1940, during an epidemic of influenza in New York, Francis and Magill independently recovered a second influenza virus also pathogenic for the ferret and mouse, but producing a much milder disease in these animals. Serological study showed it to be quite unrelated to the previously known virus, which was renamed influenza virus A. The name influenza virus B was given to the new agent, and serological study showed it to have been responsible for a spreading epidemic of influenza in California in 1936 and for sporadic cases during the 1939 epidemic of influenza in Britain. But influenza B was not incriminated in cases of febrile catarrh or A.R.D., whose ætiology remained undefined. Its discovery had the important effect of showing the ætiological diversity of epidemic influenza, which has been abundantly confirmed since. The two viruses are apparently distinct epidemiologically and immunologically. Recently a third type of virus (1233) was recovered by Taylor (1949) from a sporadic case of influenza in 1947. This virus was unrelated either to influenza virus A or B, and doubt existed for some time concerning its true nature. Its chief claim to the name influenza virus was that when cultivated in the fertile hen's

egg it had certain biological characters resembling those of the other influenza viruses. But the same could also be said of the mumps virus. In 1950 Francis and others described the isolation of another strain of virus similar to the 1233 strain and produced serological evidence of infection by the virus in children The cases of infection with the virus occurred at the same time as cases of influenza A and resembled influenza clinically. The name influenza virus C is therefore proposed for the new strain, and it is, of course, far too early to foresee the clinical and epidemiological characters appertaining to the agent (Taylor, 1951).

Meanwhile, during the second world war intensive studies of outbreaks of respiratory disease among soldiers in the U.S.A. led to an advance in knowledge concerning the clinical features of undifferentiated acute respiratory disease unassociated with the influenza viruses Certain patients with symptoms of upper respiratory tract disease, but also with cough and sputum, were found to have radiological evidence of extensive pulmonary involvement. A similar clinical syndrome had been encountered in 1934

conditions were ætiologically similar was soon dispelled by the evidence that some cases could be shown to be due to infection with a virus of the general group of psittacosis-ornithosis Towards the end of the war, *Rickettsia burneti* was also found to produce a closely similar clinical picture However, the main mass of cases among military establishments gave no evidence of infection with these or other ætiological agents Studies on human volunteers by Dingle and his associates (Commission on Acute Respiratory Diseases, 1946), indeed, suggested that infection by a filterable virus was concerned in

that psittacosis, ornithosis and Q fever are specific examples of ætiologically defined conditions capable of producing the syndrome. By far the greater number of cases remain ætiologically undefined, however, and as these increase in incidence during outbreaks of febrile catarrh (A R D), it seems desirable to classify these cases within the latter group

A further subdivision on clinical grounds was the recognition of a pharyngitis with visible exudate on the fauces, so that the group of acute respiratory disease unassociated with defined ætiological

CHAPTER 2

CLINICAL PICTURE OF INFLUENZA

EPIDEMICS of influenza may occur as small outbreaks in communities of a few hundred persons, or may sweep remorselessly through the towns and countryside of entire continents. The disease has at times appeared so unexpectedly as to suggest a visitation from without, and its arrival was regarded with feelings of terror during the successive waves of the 1918–19 pandemic.

Yet recent epidemics in Great Britain and elsewhere have been so mild by comparison as to raise doubt concerning their genuine relationship to the great pandemics of the past. However, when towns such as Paris or Rome report an incidence of 20 per cent of infections in their population—as happened, for instance, in 1949—it is not easy to dismiss the condition either as trivial or unimportant. The cost to the community of such an epidemic can be measured in terms of human misery or by its effect on the industrial life and economy of the nation. Certainly, the rise in the death-rate, and particularly in the deaths of infants or of the aged, cannot be taken as the sole indication of the severity of an epidemic, impressive though this may be. It is the power of influenza to cause simultaneously increased numbers of illnesses over a wide area which is responsible for its disruption of normal life. Practitioners who visit homes only to find whole households in bed, or whose surgeries are bethronged with crowds of sufferers, know the effects of an influenza epidemic only too well. In Liverpool during the 1951 epidemic even hospitals were disorganised by the simultaneous influx of patients and widespread sickness in the nursing staff.

The clinical picture of influenza as witnessed during large outbreaks was described years before the influenza viruses were known. The recovery of these agents did nothing to destroy the validity of this picture as representative of the mean or average illness associated [illegible] If it is now understood that [illegible] ·cks [illegible] nts, there is no harm in continuing to regard the picture of clinical influenza as an entity. There is, in fact, a typical and historic picture of influenza which is seen in a proportion of cases during all types of influenza virus epidemics, and which presents a certain degree of

clinical contrast with other respiratory tract syndromes. The [illegible]

[illegible]

The clinical picture of uncomplicated influenza

Onset. The incubation period lasts from twenty-four to forty-eight hours, or occasionally for three or four days, and terminates in a sudden onset of illness with headache or shivering. Sometimes a vague onset occurs after premonitory symptoms of a cough, sore throat or cold More often patients can tell the hour of onset by a sudden backache, or headache, or sneezing. Rarely, a fainting attack may be the initial symptom, and in 1937 a soldier was observed who was admitted to hospital with a broken jaw resulting from fainting on the parade-ground The commonest combination of symptoms at the onset of influenza is headache and shivering, but headache and cough or headache with nasal symptoms are also seen. Sore throat is not common as an early symptom.

General course of illness Following the initial symptoms of illness, the patient usually recognises a rapid worsening of his condition, with headache, anorexia, prostration and muscular aching. Limb and back pains are not so prominent in children or young adults as in older persons, and in general the degree of constitutional involvement and symptomatology increases with age The temperature rises sharply to a peak, and thereafter takes one of several courses It may decrease progressively in step-ladder fashion, it may fall precipitately only to rise again on the third day so as to give a diphasic curve, or it may vary in a totally irregular fashion The total duration of fever averages seventy-two hours, but many pyrexias last only forty-eight hours, and the average of three days is perhaps the result of the occasional prolongation to five or seven days.

Once the temperature has reached its peak, constitutional symptoms diminish and symptoms arising from the respiratory tract become more prominent The nose is either running or blocked, cough is invariable, but sputum is raised in less than one-third of uncomplicated cases of influenza The question of sore throat is a difficult one Many patients deny that their throat is sore, though they may say that it feels dry, but in about 40 per cent of cases some degree of soreness is admitted The voice is not often a source of

complaint, and aphonia, though occasional, is not common; yet some change in voice, so that there is huskiness or hoarseness, may be observed in about half the patients Chest pain, usually substernal in location, is felt in about a quarter of the patients.

Throughout the fever there may be continuing headache or muscular pains, the appetite is lost, there may be slight nausea and sleep is disturbed. Vomiting, though it may usher in the attack, is not a common symptom. Diarrhœa has not occurred during influenza virus outbreaks investigated by the author, but occasional cases of Sonne dysentery may occur admixed with cases of influenza, and cause confusion.

Table 1 compares the frequency of the various symptoms ex-

TABLE 1

Symptomatology of Influenza A (Percentage Frequency)

	1937 epidemic (Stuart-Harris *et al.*, 1938) 84 cases	1943 epidemic (U S Commission on Acute Respiratory Diseases, 1948*a*) 79 cases.	1947 epidemic (Kilbourne and Loge, 1950) 76 cases
Sudden onset	75	35	66.6
Malaise	91	70	Feverishness 98.5
Headache	87	76	86
Anorexia	77	75	—
Shivering	74	77	86.5
Coryza or nasal obstruction	73	Sneezing 59	Nasal disch. 70.3
		Nasal obst 81	
		Nasal disch. 77	
Cough	71	84	97 (Dry in 61.6)
Dizziness	62	—	—
Muscular pains	51	—	66.8
Sore throat	43	42	49.4
Ocular symptoms	33	—	Burning eyes 57.6
			Aching eyes 62.4
			Eye disch 30.8
Insomnia	32	—	—
Sweating	31	—	—
Expectoration	31	35	32.8
Pain in the chest	24	57	45
Epistaxis	21	—	13.1
Constipation	21	—	—
Nausea	21	—	29
Vomiting	11	—	9.2
Dyspnœa	11	—	—
Abdominal pain	8	—	14.5
Hoarseness of voice	6	53	—
Observed alteration of voice	58	—	—
			General ache 60.0
			Dry throat 26.1
		—	Diarrhœa 4.0
Fainting	4		—
Faint feeling	2	Weakness 80	—

pressed as a percentage in three groups of patients—all servicemen in British or U.S Forces The British series comprised 84 cases studied in 1937—not all of whom were proved by laboratory tests to have influenza. The sharpness of the epidemic and the uniformity of the clinical picture were earnest of the high probability that influenza virus infection existed (Stuart-Harris, Andrewes and Smith, 1938) The two American groups of cases were those studied in 1943 during a widespread epidemic and in 1947 in localised outbreaks. All three were epidemics of influenza A, though that in 1947 yielded a virus with the antigen designated A prime (Chapter 5, page 84) The table shows a good deal of agreement between the series of cases, but some points of contrast exist. Sudden onset was more frequent in the British cases and in the American 1947 cases than in the 1943 epidemic. Muscular pains were not mentioned by the 1943 observers, but were noted in both the other series of cases. Agreement in regard to respiratory tract symptoms was remarkable, and the only point of contrast was the more frequent finding of substernal chest pain in the American cases The general findings support the view already expressed that there is a recognisable symptomatology among cases of influenza virus infection.

Physical signs. French (1920) described a characteristic facies in the cases of influenza seen during the epidemic of 1918, which began as an appearance of red flushing of the face and later changed to a heliotrope coloration with an extremely toxic appearance. This facies has dominated the many clinical descriptions of influenza in the past, but though seen in occasional individuals in recent epidemics, it is in fact uncommon A more common appearance seen during epidemics of influenza among servicemen is one of extreme weariness, with flushing of the face at the height of the fever There may be slight cyanosis of the lips of peripheral type, and the patient, if undisturbed, has no desire to interest himself in any activity other than sleep. A comment of an R A F officer who saw the first cases from whom influenza virus was obtained during the epidemic of [illegible]

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and dry. The pharynx varies greatly in appearance, being in some normal, in others injected with prominent vessels and swollen adenoid tissue and in a few patients a dry, granular appearance of the posterior pharyngeal wall may be seen. Exudate of any variety is uncommon, but a blob of greenish mucus may be present in the post-nasal space, having been extruded from the posterior nares Adenitis in the cervical region is not prominent, though tonsillar glands may be slightly swollen. The voice is often affected as noted above, but actual aphonia is not common.

The chest may be clear of physical signs throughout the illness, but in about one-third of cases of ordinary uncomplicated influenza there may be a few loose râles or scattered rhonchi, which do not persist for long. In such patients there may be a productive cough with greenish mucopus often coughed up in discrete pellets; in general, however, the cough is dry.

The pulse varies greatly, and tachycardia of slight degree is more common than a relative bradycardia True bradycardia is common, however, in the early days of convalescence.

The blood-pressure may be slightly raised during the fever, but falls during convalescence.

The tongue is frequently coated, the bowels are constipated, but the abdomen is normal The urine is usually normal, and

TABLE 2

Physical Signs in Uncomplicated Influenza A (Percentage Frequency)

	1937 epidemic (Stuart-Harris *et al.*, 1938) 82 cases.	1943 epidemic (U.S Commission on Acute Respiratory Diseases, 1948*a*) 79 cases	1947 epidemic (Kilbourne and Loge, 1950) 76 cases
Flushed face	67	45	58
Cyanosed lips	41	—	—
Conjunctival abnormality	89	46	66 2
Nasal obstruction	51	68	—
Nasal discharge	22	61	52·4
Epistaxis	15	—	—
Furred tongue	46	—	—
Injected pharynx	73	39	72
Faucial exudate	1	—	—
Cervical gland enlargement	38	—	21 7
Abnormal chest signs	23	40	3 9
Sputum	31	35	32 8
Duration fever	3 6 days	—	2 3 days
Maximum temperature (average)	101 2 F	100–102 F	101 3 F

albuminuria, if present, is not more than that associated with any fever.

The frequency of the various physical signs during the 1937 epidemic is contrasted in Table 2 with those found in a similar study in 1943 by the Commission on Acute Respiratory Diseases (1948*a*) and during the influenza epidemic of 1947 by Kilbourne and Loge

The general course of the disease is illustrated by the following four cases (1 to 4) taken from outbreaks of influenza A in 1937 and 1951 It must be understood that precisely similar cases have been encountered during outbreaks of influenza virus B infection

Illustrative cases of influenza A

CASE 1. *Simple influenza.*

W. J B , aged 21, R A F. serviceman, admitted twelve hours after the onset of illness, which occurred suddenly with headache, backache and aching round the waist and in joints. Slight cough and nasal discharge did not interfere with sleep On the morning of admission, aching,

and the pharynx injected and reddened with engorged vessels but no exudate The course of the fever is shown in Fig 2 The patient felt better on the third day, when the temperature had fallen , the nose was now blocked, the throat still injected but not sore Cough and sputum were absent and there were no abnormal signs in the chest. By the sixth day of illness the patient felt quite well, but the temperature was still irregular, the nose was still slightly blocked and he had an occasional cough Convalescence was uninterrupted from the seventh day of illness onwards. Influenza virus was recovered from the patient's garglings on the second day of illness (ferret inoculation)

CASE 2 *Influenza with catarrhal symptoms*

Miss A M , aged 19, domestic servant, was admitted on the second day of an illness w

turbed sleep

pain in the bac

running nose ar

nt was 4,550 per cu. mm on the
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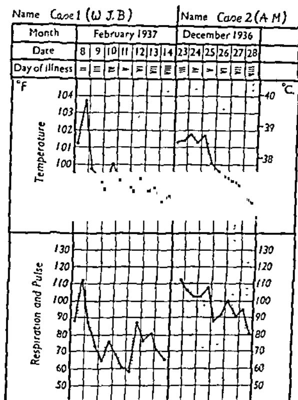


FIG 2 FIG. 3

CASE 3. *Influenza with signs in the chest.*

Miss J J , aged 18, a student, began to be ill with a sore throat, followed by a cough, five days before admission to hospital. Two days later she reported her illness because she felt feverish and had continued sore throat and cough. No pyrexia was found, but that evening she shivered, and in the morning her nose began to run, her eyes felt sore and there was continued shivering Pyrexia was first recorded on the day of admission, *when she complained of dizziness, severe frontal headache and photophobia* On admission temperature was 104° F and pulse 128. Cough was accompanied by some greyish sputum, and there was a tight sensation over the sternum There were aching pains in the knees, ankles and elbows She was thirsty but had no appetite.

Physical signs were slight She was flushed but not cyanosed. The eyes were bright Tongue was furred. The pharynx was not abnormal.

...sional
The
... exam-
... after
admission râles persisted, the leucocyte count was 4,700 per cu. mm and the sedimentation rate was raised to 36 mm (Wintrobe) Thereafter convalescence was uninterrupted Influenza virus was recovered from

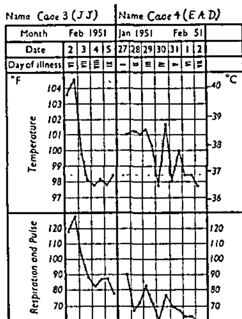


Fig 4 Fig. 5

gargling collected on the day of admission by injection amniotically into fertile hens' eggs This patient gave a history of frequent attacks of bronchitis as a child.

Case 4 *Influenza with signs in the chest*

E. A. D ...
influenza ...
muscular ...
(Fig 5) ...
to be ...

seventh day and recovery was rapid. Although continued cough and

sputum were prominent symptoms, this patient had had no previous chest disease.

Influenza virus A infection was proved by a significant sixteen-fold antibody rise during convalescence demonstrated by complement-fixation test; no attempt was made to recover virus from the throat.

These four cases illustrate respectively the uncomplicated "typical" attack (Case 1), the attack with "catarrhal" symptoms including sore throat, hoarse voice and epistaxis (Case 2), and attacks accompanied by minor physical signs in the chest (Cases 3 and 4). The two latter cases could be considered as having complicated influenza, but it must be appreciated that no hard-and-fast line of separation exists between the average attack of influenza and that considered to be a case with chest complication.

Pathological findings Finally, to complete this account of the physical findings in influenza, some reference to pathological findings is necessary. No one, in fact, knows the morbid anatomical findings in simple influenza. Clinical evidence suggests that the nasopharynx bears the brunt of the attack. On the analogy of the lesion produced by influenza virus in experimental animals (see Chapter 4), it is to be expected that there is a necrosis of ciliated columnar epithelium with underlying subepithelial congestion and infiltration with polymorphonuclear leucocytes. However, no one can be sure how far this process extends down the respiratory tract, though it is almost certainly present in the pharynx and posterior nares. Some, indeed, hold that the initial lesion is located in the bronchus or trachea and that the virus infection spreads up the respiratory tract in a centrifugal manner. In support of this view is the fact that the movement of the sheet of respiratory mucus is normally upwards rather than downwards The early appearance of cough also favours this view, but if there is such an early lesion of the bronchial mucosa it must be patchy, or else physical signs in the chest would be likely at an early stage of the disease

Wherever the primary lesion is located, however, it is clear that the infection remains localised to the respiratory tract mucosa for which influenza virus exhibits a specific affinity. There is no evidence of any systemic invasion beyond the respiratory tract. Virus has not been recovered from the blood either in human or experimental influenza. But toxic effects are demonstrable experimentally with large concentrations of live or partly killed (inactivated) virus, and no doubt many of the constitutional symptoms of influenza are to be explained on the basis of absorption of cell and virus products from the respiratory mucosa.

The blood count is not significantly altered in uncomplicated influenza. Most studies which reported the finding of a leucopenia [illegible]

equally possible that some strains of influenza virus may cause an infection accompanied by a significant reduction in the leucocyte count, and that others may not. Henle and his fellow-authors (1946) have carried out extensive experiments on human volunteers exposed to influenza virus in the form of a mist of atomised droplets When influenza B was inhaled by the volunteers some decrease in the leucocyte count occurred on the third day, though usually not below 6,000 per cu. mm. With another strain however, this time of influenza virus A, counts as low as 2,000 per cu. mm. were commonly encountered on the third or fourth day after infection. Yet another strain of influenza A caused no change in the leucocyte count.

To the clinician the real significance of the leucocyte count is that the presence of a leucocytosis suggests the existence of a complication or of some other disease, the finding of a normal or reduced count is not of use in the differential diagnosis of influenza virus infection from other respiratory tract infections

The erythrocyte sedimentation rate is not altered during the febrile stage of influenza, but may rise slightly during convalescence As in the case of the leucocyte count, the finding of a considerable increase in the sedimentation rate should suggest the possibility of a complication or of some other disease.

The nasopharyngeal bacterial flora is not altered significantly in uncomplicated influenza Details connected with the recovery of virus from the throat and demonstration of the development of antibodies will be found in Chapter 5.

Sequelæ and complications The belief that influenza is likely to be followed by a train of symptoms and complications with particular frequency of post-influenzal debility and depression is deeply rooted The author's experience has not confirmed the view that there is any specific relation between influenza virus infection and depression. But any minor respiratory infection, even a severe common cold, may cause an upset of this character, particularly if it causes a prolonged cough or sputum The degree of prostration during simple influenza varies greatly from case to case, but it seems reasonable that sequelæ are more likely in those originally

affected severely by 'toxic' effects of the infection. Certainly school children and young adults in the Services recover from influenza with remarkable rapidity and usually exhibit no sequelæ. The middle-aged and elderly, however, take longer to recover, particularly if they already suffer from some condition such as chronic bronchitis. In any case, and even in younger subjects, cough is the last symptom to disappear and may last at least a week after other symptoms have cleared up

Relapses of a minor febrile character are occasionally seen, but these are usually commoner in those originally exhibiting signs in the chest during the original attack. Sometimes the second attack is indistinguishable from the earlier one, but in others a frank tonsillitis, perhaps with hæmolytic streptococcal infection, occurs during convalescence from influenza.

Sinusitis and otitis media are occasional sequelæ to influenza Their frequency is not considerable, but they are, of course, troublesome complications. The various complications of influenza concerned with the chest are fully described in Chapter 3.

The range of infection with influenza virus

There is general unanimity among those who have described the clinical events during epidemics proved to be due to the influenza viruses that a great diversity of clinical manifestations is witnessed. This is not surprising when it is realised that the virus infection may be entirely subclinical, associated with a minor febriculum, a fever of three to five days' duration, pyrexia with various grades of bronchitis or pneumonia or a rapidly fatal illness in which the patient is dead almost before there is time for symptoms and signs to be exhibited

Possible modifications in the clinical picture of those infected may result from variations in the pathogenic properties of the strain of virus concerned. But the varied and differing degrees of pre-existing experiences of the virus by the human hosts with their resultant grades of partial immunity are further important factors which impose a rich variation in clinical phenomena.

(1) *Subclinical infection.* It has already been stated that serological examination of various individuals during an influenza epidemic shows a much wider range of infection than would be suspected on clinical examination alone. In the first place, numerous observers have obtained evidence that during an epidemic entirely silent infection is a frequent occurrence Opinions vary concerning the exact frequency of such subclinical infections, and it is probable

that no constant percentage of individuals suffer infection in this manner. By using the complement-fixation method for the demonstration of antibodies, Hoyle (1944) concluded that at least 23 per cent of the community had been infected during the 1943 epidemic and that the figure might have been even higher. Even if 10 per cent of the population had experienced clinical illness (and this would be a high figure for a population other than that of an institutional group), this would mean that at least 13 per cent of the community had experienced subclinical infections. The Commission on Acute Respiratory Diseases (1948*b*) concluded that [illegible]

During 1949, both before and after the epidemic of influenza A, a random collection of sera was made in the North of England and sera were examined for the presence of antibodies to the particular infecting strain of the epidemic (an influenza A prime virus). Using the agglutination-inhibition test, antibody levels in the range above that of the normal serum level increased from 4.9 per cent before to 18.1 per cent after the epidemic, thus suggesting that at least 13.2 per cent of the population had been infected. This method suffers, however, from the difficulty in differentiating the normal serum inhibitor from anti-viral antibody, and therefore may have failed to indicate the true percentage of infection. In 1951 sera were collected before, during and after the epidemic from individuals entering hospital in Sheffield for various types of surgical operation. Sera were collected from the same individuals seven or more days later, and the pairs of sera from each individual were examined by the complement-fixation test. Three of 72 individuals thus examined showed a four-fold or greater increase in antibody in the second of the pair of sera, and none of these individuals had any clinical symptoms which could be categorised as influenza during their stay in hospital. Such subclinical infection might have been contracted, of course, either before admission or while in the hospital. The distribution of complement-fixing antibody titres in the first sera of the individuals also underwent a change during the period of the study (Fig. 6).

Fig. 6 shows that there was no detectable complement-fixing antibody in 39 of the first 50 sera collected in January, before the influenza epidemic had reached its peak. During February and early March, however, only 25 of the 55 sera which were collected

failed to give fixation of complement. Thus at least 32 per cent of the population from which the patients were drawn had undergone some specific serological change. Titres of 8 or more increased from 3 per cent in the first 50 sera to 25 per cent in the second sera. It would be reasonable to conclude, therefore, that between 23 and 32 per cent of the population experienced infection with the virus during the period of the study Yet only two or three patients admitted, at the time of entry to hospital for their surgical conditions,

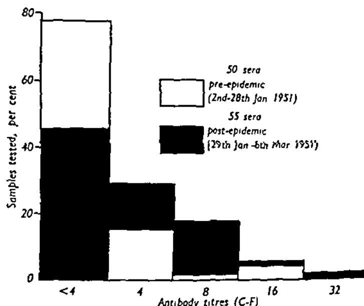


FIG. 6 —Distribution of influenza virus A antibodies in surgical patients admitted to hospital before and after an influenza epidemic

Columns show the percentage number of sera with complement-fixing antibody titres in the particular category The antigen was derived from infected egg membranes ("soluble" A antigen)

that they had recently experienced an influenzal illness It should be pointed out that all these instances of subclinical infection which have been quoted have been derived from moderately severe epidemics of influenza A. The percentage of individuals suffering subclinical attacks might be much lower when the fire of infection in the community is burning less brightly.

(ii) *Mild febricula* There is no simple description of the mild attack of influenza which covers all the various clinical possibilities All outbreaks of influenza cause an increase in the number of those with simple colds, or trivial sore throats, or one-day fevers with

headache and aching, or of cough. It is usually impossible to [illegible]

[illegible]

The following two cases illustrate the minor febriculum of influenza.

CASE 5 *Trivial influenza.*

J. J. G., aged 18, student, complained of a headache, heavy eyes, a [illegible]

[illegible]

CASE 6. *Trivial influenza*

A. H., aged 22, student, reported on 30th January 1951 because of a [illegible]

[illegible]

obtained at the onset.

The deliberate infection of volunteers with influenza virus throws some light on the clinical phenomena of natural influenza Usually no constant clinical event follows the nasal instillation of liquid containing influenza virus cultivated in the laboratory When the liquid is atomised, however, so that the volunteers inhale a mist, a considerable proportion of normal individuals develop an infection Clinically, this is usually a one- to three-day fever, with shivering, headache and malaise Minor flushing of the pharynx, cough and physical signs in the chest may be found However, there are many minor variations of the infection, and American authors (Francis and others [illegible]

[illegible]

Virus preparations rendered non-infective and inhaled in the same manner do not cause febrile reactions, so that the mild reactions observed must indicate some form of response to living virus, and it is conceivable that they may in fact be allergic in origin

(iii) *Gastric and nervous forms of influenza* Gastric 'flu is a familiar diagnostic refuge for cases of unexplained vomiting, perhaps with pyrexia and tendency to spread throughout the family All that is definitely known concerning the relation to influenza is that influenza virus infection can be accompanied by vomiting, particularly

at the onset of the disease. On the other hand, persistent vomiting is not common, and diarrhœa is most exceptional. It seems unlikely that outbreaks of vomiting are in fact related to influenza. Certainly the epidemic nausea and vomiting described by Bradley (1943) must be due to an entirely different agent or group of agents, if it is an infection at all (Pickles, 1944).

The following case-report in a case of influenza A seen during the 1937 epidemic should serve to illustrate early gastric symptoms.

CASE 7. *Influenza with gastric symptoms.*

N. C. G, aged 18, soldier, began to shiver and feel ill on the day before admission. There was a headache, slight nasal discharge and

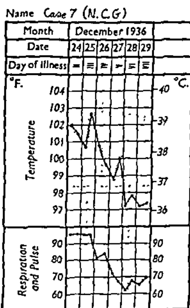


FIG 7

during the night vomiting at frequent intervals. By the next day he had vomited twelve times, still felt shivery and ill with a headache. Vomiting occurred once only after admission. There was no abdominal pain

(ferret inoculation)

It is customary to regard influenza as being occasionally witnessed in a 'nervous' form This is probably due to the occasion of febrile illness, often termed influenza, at the onset of encephalitis

lethargica. Moreover, considerable epidemiological speculation [illegible]

probably do not occur, but sporadic cases of encephalitis, often accompanied by a lymphocytosis in the cerebrospinal fluid, are seen endemically in Great Britain If such sporadic cases occur at a time when influenza virus infection is rife in the community, the possible ætiological relationship of the two circumstances arises. There is no positive evidence of a relationship, however, and it seems more reasonable to regard sporadic encephalitis as being due to some other as yet unidentified neurotropic agent. Probably the fact that strains of influenza virus can be rendered neurotropic in the laboratory (Stuart-Harris, 1939) should prevent any dogmatic statement that influenza can never cause encephalitis. If a mutant strain with neurotropic properties arose in natural circumstances, it would not be likely to be missed at the present time. No such strain has in fact been encountered. In the meantime it must be stated that cases of obscure nervous disorder such as polyneuritis and encephalitis may appear in increased numbers during or after an outbreak of influenza Such have been recorded in recent years by Leigh (1946) and Jennings (1952). If more was known concerning the ætiology of sporadic cases of similar nervous manifestations which may occur at any season or in any year, it might be possible to speculate upon the connection, if any, between neurological disease and influenza

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CHAPTER 3

CHEST COMPLICATIONS OF INFLUENZA

THE statistical hall-marks of epidemic influenza are: firstly, the rise in the death-rate from all causes, and particularly from respiratory conditions, and secondly, the increased incidence of pneumonia. These two characters serve in some measure to distinguish *influenza virus infection* from other infections of the respiratory tract. But when clinical observations are made on a community during a sharp outbreak of influenza, they result in the assemblage of a bewildering group of conditions Indeed, every variety of case of lower respiratory tract disorder is seen, from a trivial bronchitis to various grades of acute pneumonia. The clinician working in a hospital or in the home, without resort to radiological assistance, may also conclude that he is more often dealing with pneumonic consolidation as a complication of influenza than is in fact the case. Thus many cases of acute involvement of the lower respiratory tract resemble cases of pneumonia clinically, yet *resolve with considerably greater rapidity and fail to show* abnormal radiological appearances. Probably such cases swell the list of notifications of acute primary or influenzal pneumonia which furnish the *Medical Officers of Health* and the *Registrar-General* with statistics of pneumonia morbidity At any rate, the findings in the City of Sheffield during four winter seasons from 1947 to 1951 may be given in full as an illustration of the phenomenon.

Figs. 8 and 9 show the actual notifications of pneumonia in 1947–51 in Sheffield viewed in perspective against the background of the recorded deaths from influenza in the Great Towns of England and Wales As will be shown later, these deaths afford good evidence of the prevalence of influenza virus infection. The winter 1948–49 was one in which influenza deaths showed hardly any seasonal rise and in which influenza virus infection was not encountered in laboratory tests. Pneumonia notifications in this winter give a useful background experience in the absence of influenza Peak figures were recorded in December and January, and the level of notifications during the rest of the winter formed a plateau. The winter of 1949 furnished a contrast, in that a sharp epidemic of influenza developed in February and March and influenza virus A prime was recovered from numerous cases in Sheffield from the

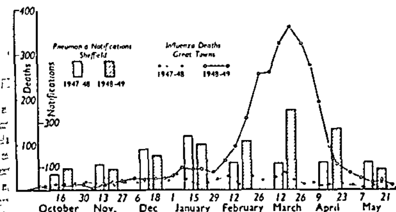
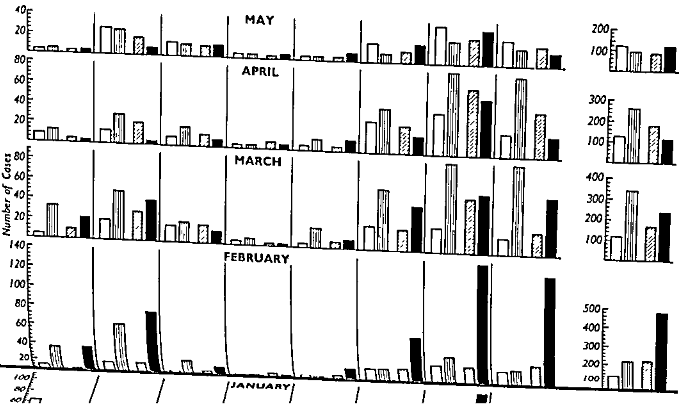


FIG 8.—Monthly notifications of pneumonia in Sheffield and weekly influenza deaths in the Great Towns (England and Wales), 1947–49

FIG. 9.—Monthly notifications of pneumonia in Sheffield and weekly influenza deaths in the Great Towns, 1949–51



MAY
APRIL
MARCH
FEBRUARY
JANUARY
Number of Cases

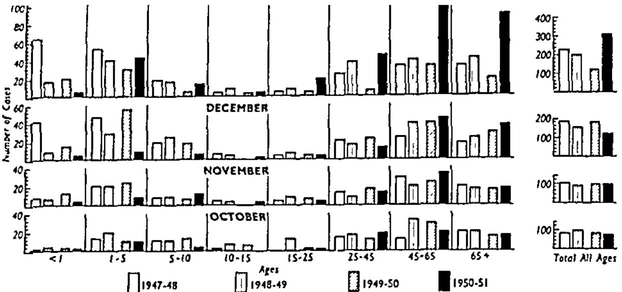


FIG. 10.—Age distribution of pneumonia notifications in Sheffield, 1947–51

Columns indicate the numbers of notified cases of pneumonia arranged by age and by month in each of the four seasons beginning in October and ending in May

middle of February onwards. Pneumonia notifications rose to a peak in March, and the figures for December and January were actually lower than in the preceding winter.

The winter of 1950 was not accompanied by a sharp outbreak of influenza, but school epidemics of influenza B occurred in the vicinity of Sheffield in February, and the deaths from influenza reached a peak in March. Pneumonic notifications remained at a relatively low level throughout the winter, and the figures for pneumonia in Sheffield were the same in December 1949 as in April 1950. However, 1951 again produced a sharp epidemic of influenza in the community, and numerous cases of influenza virus A prime infection occurred in Sheffield in January and February. Notifications of pneumonia rose to a sharp peak in February, the figure being the highest in any of the four years

Age incidence of chest complications

The notifications from pneumonia also afforded an indication of the age distribution of the pulmonary complications of influenza (Fig. 10). Thus, in March 1949, when influenza virus infection was rife in the community, it is clear that the major numbers of cases of acute pulmonary disease occurred in those aged 45 and over. Although a rise occurred in the number of notifications in children aged 1–5 in February 1949, the number in infants under 1 year of age was not as high as in the corresponding period of 1948. Indeed, it seems from the chart that a considerable number of cases of baby pneumonia occurred in 1948, at a time when influenza virus could hardly have played any significant part in the ætiology. In January and February 1951, during the prevalence of influenza A, notifications of pneumonia rose sharply both in children aged 1–5 and in those aged 45 and over.

These age-periods of maximum prevalence of notified cases of pneumonia at the time of influenza epidemics throw into sharp relief the low incidence in the age groups 10–25. Moreover, the figures for ages 25–45 are no higher than those for the ages of 1–5. It is therefore apparent that if notifications from pneumonia may be taken as an index of the pulmonary complications of influenza, the ages most affected during recent experience have been those of 45 and over So far as children are concerned, those aged 1–5 are probably more involved than babies or older children In the absence of exact figures of age distribution in the community in Sheffield, it is not possible to calculate exact incidence. Mortality from pneumonia in relation to influenza epidemics will be considered in

the section dealing with deaths from influenza (Chapter 6) It is clear that the deaths chiefly occur in those of 65 and over, so that although there are many cases of pneumonia in those between 45 and 65, these do not result in death so frequently Possibly this is a reflection of the degree of ineffectiveness of antibiotics and chemotherapy in the pneumonias of elderly subjects.

Clinical varieties of chest complications

For descriptive purpose three different categories of complications can be recognised. These are:

(i) Influenzal bronchitis and bronchiolitis
(ii) Influenzal pneumonia
(iii) Post-influenzal and other varieties of pneumonia.

In both groups (i) and (ii) influenza virus infection leads on to the complication without pause, but in group (iii) the virus infection either precedes the pneumonia by some days or accompanies it.

Influenzal bronchitis and bronchiolitis. No sharp distinction exists between cases of influenza with simple cough and sputum and those considered to have a definite bronchitis. But, proceeding from the mild cases to others with persistent râles in the chest and protracted cough, grades of increasing clinical severity can be discerned At the severe end of the scale are illnesses little short of pneumonia, yet without any radiological confirmation of consolidation It is difficult to know the frequency of this entire group of cases Among the group of 120 servicemen studied during the 1937 epidemic, 82 were classified as simple influenza, and of these 19 (23 per cent) were found to have definite signs in the chest But 17 others from among the 120 men and boys were classified as definite cases of bronchitis and bronchiolitis The majority of these men seen by the author in the Services had no pre-existing history of chest disease

In the recent series of 223 cases of influenza studied in 1951 in a general practice by Fry, 37 developed physical signs in the chest, 4 only of whom showed consolidation All but 6 of these patients had a clean medical history However, it must be admitted that a high proportion of those entering hospital during an epidemic have a past history of chronic disease either of the chest or cardiovascular system It is difficult to build up a clear picture of the clinical condition in such individuals

The occurrence of a definite chest lesion in previously healthy individuals is indicated either by an unusual degree of toxæmia and

cyanosis or by early dominance of the illness by cough and sputum. In either case the temperature usually fails to subside by the third day, and fever may be continued for a week or more. Occasionally it falls and then rises irregularly each evening The symptoms are initially those of influenza, but later productive cough becomes more in evidence. Sputum, which is raised often with difficulty, may be in the form of pellets of yellowish or green mucopus Sometimes it is blood-streaked. Pain in the chest may occur, but is a dull mid-sternal or lateral sensation rather than a sharp pleural pain, except in the occasional case with pleural involvement. Dyspnœa occurs in those with bronchospasm as shown by the use of accessory muscles of respiration, wheezing and expiratory rhonchi But it may also develop in those with severe bronchiolar involvement, and it is then a major source of confusion with pneumonia.

Physical signs are those first of all of influenza The chest signs are usually obvious, with numerous added sounds. The cases of bronchitis exhibit rhonchi or scattered sticky râles. Breath-sounds *are often normal, but occasionally weak in scattered areas* The signs of bronchiolitis are usually found at one or both bases. Movement is diminished, breath-sounds have a suppressed quality, but *percussion note is only slightly impaired, and the dullness* of consolidation is lacking. Fine or medium râles occur in the affected areas, and may be combined with coarser râles elsewhere. The occasional patient develops pleural friction, and a small quantity of pleural fluid, usually sterile on culture, may collect. Radiological examination of the chest in all these cases is usually negative, and this is often surprising in view of the dyspnœa and abundant cough and sputum suggestive of pneumonia. During the 1937 epidemic scattered fine opacities were seen, particularly at the lung bases in some severe cases of bronchiolitis, but the picture is not constant. In others partial collapse of a lung segment may occur, but this again is infrequent

The pathological findings in these cases can only be guessed. As will be instanced later, lung lesions in mice infected experimentally with influenza virus centre around necrotic changes in the epithelium of the bronchioles. It would be reasonable to consider that similar epithelial changes *occur in man. The leucocyte count is not* usually altered significantly in cases of influenzal bronchitis or bronchiolitis The sputum shows no constant bacterial flora. *Hæmophilus influenzæ* is *more* likely to be encountered than in cases of simple influenza, and is present in [illegible] in abundance The pneumococcus, *S*[illegible]*occus* [illegible] hæmolytic streptococcus are

inconstant in the sputum in cases lacking true consolidation. Influenza virus is present in the sputum or pharyngeal washings during the early phases of the illness.

The course of illness is more protracted than in simple influenza, but ultimate recovery appears complete. A careful follow-up of such patients in order to detect possible bronchial damage would be worth while, but has not been attempted by the author. The point should perhaps be made that cases of influenzal bronchiolitis do not present the radiological findings of atypical pneumonia, and though clinical differentiation may be difficult, it is clear that influenza virus is only rarely encountered in cases of this syndrome.

Cases 8–10 illustrate moderate and severe cases of bronchiolitis in patients without previous chest disease. Cases 3 and 4, already given, illustrate mild bronchitis. None of the patients received chemotherapy.

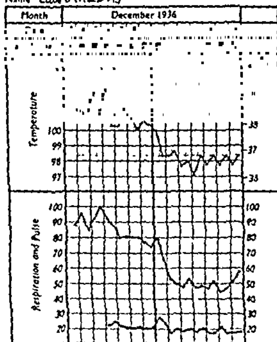


FIG. 11

CASE 8. *Influenza with bronchiolitis.*

A. W. D. A., aged 19, airman, had never been ill before. Developed headache, dizziness, nausea and shivering on the 13th December 1936 Two days later he still felt ill, the nose was blocked, there was slight cough and rhonchi were heard in the chest. On the 16th December pyrex continued (Fig. 11), the sputum was frothy and mucopurulent. T breath-sounds were weak at the left base and there were many sticky râ at both bases. Fever continued until the 20th December, when th was still cough, the sputum was green and the signs in the chest were changed. The leucocyte count varied between 7,400 and 10,000 per mm. The sputum yielded *Hæmophilus influenzæ*. Virus A was recov from garglings collected on the second day of illness. Convalesc was accompanied by a pronounced bradycardia (44–50). The chest clinically clear on the 31st December.

CASE 9. *Influenza with bronchiolitis*

B. M. R., aged 22, airman, had had no previous illness. Inf began on 13th December 1936 with sneezing, shivering, sore thro

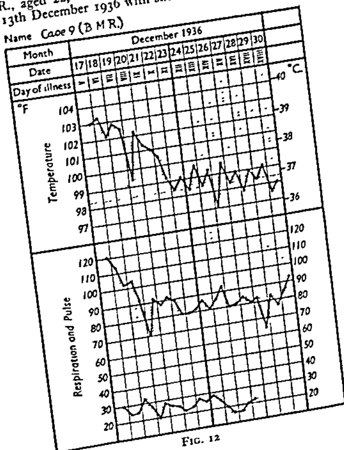


FIG. 12

cough. There was anorexia, insomnia and productive cough on admission on the 17th, when the temperature was 103° F., pulse 120 and respirations 30 The sputum was mucopurulent; there was pain anteriorly in the midline on deep breathing. Both lung bases exhibited weak breath- [illegible]

CASE 10. *Influenza with bronchiolitis and pleural effusion.*

C. F. B., aged 16, naval recruit, had had no previous illness. Influenza began on 6th January 1937 with headache and shivering, but he had had

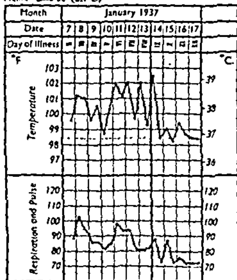


FIG. 13

some malaise for two or three days and two episodes of epistaxis. Cough and mucopurulent sputum were present. The nose was running. Fever continued for nine days (Fig. 13) and when the chest was examined on the ninth day of illness the percussion note was slightly impaired at the left base and breath-sounds were weak. There was pleural friction at the left base and râles at both bases. An X-ray showed tiny irregular miliary shadows at both lung bases and a small pleural effusion at the left base (Fig. 14).

CASE 8. *Influenza with bronchiolitis.*

A. W. D. A., aged 19, airman, had never been ill before. Developed headache, dizziness, nausea and shivering on the 13th December 1936 [illegible] from garglings collected on the second day of illness. Convalescence was accompanied by a pronounced bradycardia (44–50). The chest was clinically clear on the 31st December.

CASE 9 *Influenza with bronchiolitis*

B. M. R., aged 22, airman, had had no previous illness. Influenza began on 13th December 1936 with sneezing, shivering, sore throat and

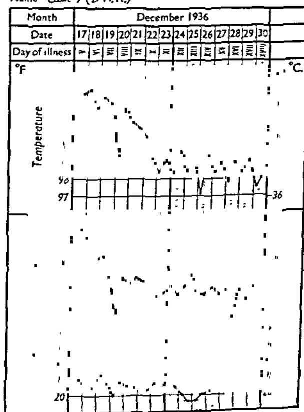


FIG 12

cough. There was anorexia, insomnia and productive cough on admission on the 17th, when the temperature was 103° F., pulse 120 and respirations 30. The sputum was mucopurulent; there was pain anteriorly in the midline on deep breathing Both lung bases exhibited weak breath-sounds and fine râles. These signs continued for ten days, and the patient became dyspnœic on mild exertion, raising green purulent sputum. Fever diminished on the 22nd, but there was irregular pyrexia for a further week (Fig 12) Green sputum yielding *Hæmophilus influenzæ*, non-hæmolytic streptococci and diphtheroids continued until 31st December. *The leucocyte count varied between 6,800 and 9,200 per cu. mm.* The patient's serum developed a sharp rise of neutralizing antibodies to influenza A as convalescence was entered (mouse neutralization test).

CASE 10 *Influenza with bronchiolitis and pleural effusion.*

C F B., aged 16, naval recruit, had had no previous illness. Influenza began on 6th January 1937 with headache and shivering, but he had had

FIG 13

some malaise for two or three days and two episodes of epistaxis Cough and mucopurulent sputum were present The nose was running Fever continued for nine days (Fig 13), and when the chest was examined on the

Though still coughing and raising scanty sputum, the patient began to improve, and convalescence was established by the sixteenth day, when the only signs were weak breath-sounds and slight impairment of percussion

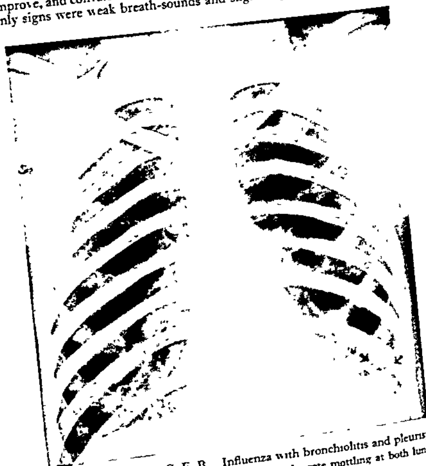


FIG 14 —Case 10 C F B Influenza with bronchiolitis and pleurisy
Radiograph on 10th day of illness, showing discrete mottling at both lung bases and opacity at left base suggestive of small pleural effusion

at the left base. The chest X-ray was clear on the thirty-sixth d (Fig 15), when the patient had completely recovered. No bacteriologi examinations were made, but the illness began at the height of the epidemic of influenza A in the naval barracks

So far the description of chest complications has been based on patients with no previous chest disease, but in those who have suffered in the past from frequent attacks of bronchitis, or who are emphysematous subjects, influenza is accompanied by a renewal o chest signs, and convalescence is much more protracted. Case 1

illustrates influenza in a man with previous chronic bronchitis and emphysema.

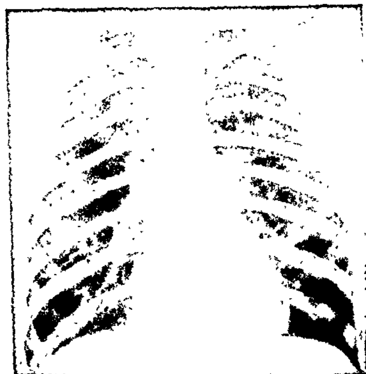


FIG. 15.—Case 10. C. F. B.
Radiograph on 36th day, showing complete clearing of lung fields.

CASE 11. *Influenza in an emphysematous subject.*

I. B., aged 46, furnaceman, had had a chronic cough, sputum and breathlessness for thirteen years. He was admitted on 25th March 1949 because of an exacerbation of cough. There was a single spike of 99° F.; he was cyanosed, exhibited expiratory rhonchi and had fine râles at both bases. The heart was normal. X-ray of the chest showed an increase in vascular markings. The patient was clinically emphysematous. The sputum was mucopurulent and contained *Micrococcus catarrhalis* and *Streptococcus viridans*. Influenza virus A was recovered from sputum collected on admission and inoculated into eggs. Wheezing and râles continued for a month. The patient's disability was then not significantly different from that prior to the influenza, and he was discharged.

from the beginning. There is no typical rusty sputum Perhaps the commonest variety is a viscid, almost stringy mucopus which may be blood-streaked. Frankly purulent sputum is also raised, and in the most severe cases sputum consists of dollops of blood mixed with mucus

The appearances of the eyes, nose and pharynx may be the same as that in cases of simple influenza, but the patient is more cyanosed. The voice may be hoarse, and there is every reason to think that the entire respiratory tract is involved in the inflammatory process The signs in the chest do not give the impression of massive consolidation confined to a lobe or a single base. Probably some dullness will be elicited and here the breath-sounds will be reduced or frankly bronchial But râles and rhonchi are usually heard in other areas, indicating the presence of widespread bronchitis Pleural friction is not usual at the onset, but may develop later. Dullness increases as the disease progresses, and may be unusually pronounced, particularly if pleural fluid collects, as it often does The amount of fluid is not usually large, though in the days before antibiotics larger effusions or empyemata were more common Radiological examination shows an opacity which may be homogeneous, but is not usually very dense in the areas where there is dullness Frequently, scattered patches of opacity are seen in other areas not regarded clinically as being involved in consolidation. The leucocyte count, though raised, is often lower than in cases of ordinary lobar pneumonia.

The resolution of the lungs is slow. In areas where opacities were present in the X-ray, focal clearing may indicate the development of lung abscesses, but it is unusual for these to be large, and they usually resolve ultimately In other cases areas of localised bullous emphysema may form, probably as a result of partial obstruction to bronchi or bronchioles This is particularly the case when staphylococcal infection is present in the lung. The patient remains weak and ill for a longer time than after lobar pneumonia, and minor relapses are common

Two illustrative cases of moderately severe influenzal pneumonia will now be described.

CASE 13. *Moderately severe influenzal pneumonia.*

Mrs J. O, aged 56, housewife, admitted on 22nd April 1950. There was a history of malaise, shivering and general aches and pains for five days. Pain in the back and cough began four days before admission. On admission she was flushed, sweating, dyspnœic and extremely ill. The temperature was 102° F, pulse 100 and respirations 35 (Fig 16). There were

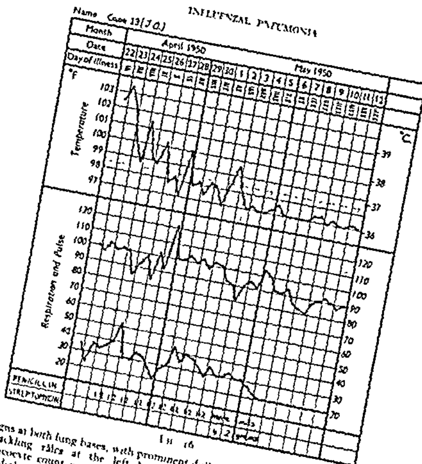


Fig 16

signs at both lung bases, with prominent dullness, bronchial breathing and crackling râles at the left base. Sputum was mucopurulent. The leucocyte count was 9 700, rising five days later to 21 000 per cu mm. Radiological examination showed irregular mottled shadows distributed chiefly at the bases and mid-zones (Fig 17). The shadowing was not homogeneous, and in the right mid-zone an area of central clearing suggesting a small abscess developed during the next week (Fig 18). The temperature did not respond sharply to penicillin treatment, and the patient remained very ill for four days, with little change in the physical signs. Slow progress towards recovery then began and after a further week of illness convalescence was entered without fresh complications. X-ray taken one month after admission still showed opacity in the original areas affected by consolidation but two weeks later the shadows had largely resolved (Fig 19). Culture of the sputum showed a *Staphylococcus pyogenes* as the predominant organism. The sputum was not cultured in eggs but the serum developed a high titre of complement-fixing antibody for influenza virus B as the patient recovered. There was no general



FIG 19 —Case 13 J O

Fig 17 Radiograph on 17th day of illness Mottled shadows are present in both lung fields, particularly in the mid-zones and left base Areas suggestive of localised bullous emphysema in the right mid-zone and left base

Fig 18 Radiograph 8 days later, on the 25th day of illness Some clearing of opacities left lung Right upper zone shows central clearing of an opacity near the periphery which may be a small lung abscess

Fig 19 Radiograph 2 months after original illness, showing complete clearing of lung fields

epidemic of influenza at the time of admission of this patient, but localised outbreaks of influenza B had been observed in school-children during the preceding period

CASE 14 *Moderately severe influenzal pneumonia*

L. B., aged 53, steel-worker, admitted on 26th January 1951 He developed a cold ten days before, and took to bed four days later because of headache, cough, sputum and severe pain in the back and chest, made

worse by breathing. Repeated shivering attacks were unaffected by treatment with sulphonamide tablets. On admission the temperature was 102·6° F., pulse 100 and respirations ... shed, There ... The

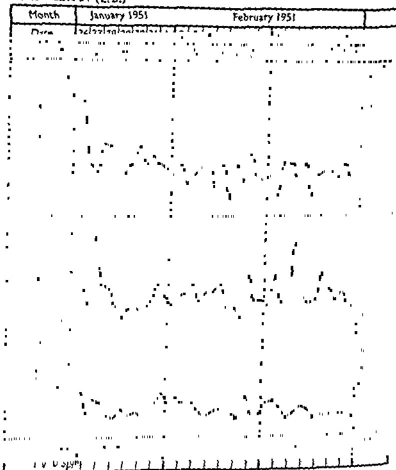


FIG 20

left chest ten days after admission gave only a few drops of bloodstained fluid. Radiological examination (Figs 21 and 22) showed shadowing in



FIG. 21.—Case 14. L. B. Moderately severe influenzal pneumonia

Radiograph on the 11th day of illness, showing streaky opacity left upper lobe and left and right bases. There is enlargement of the hilar shadows and elevation of the left diaphragm.

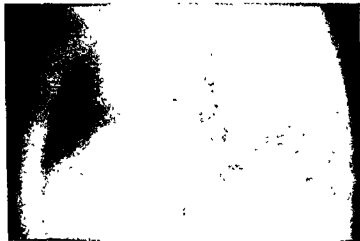


FIG. 22. Case 14. L. B. Lateral radiograph at the same time as Fig. 21.

The elevation of the diaphragm is accompanied by a zone of opacity in the supra-diaphragmatic region and a dense opacity in the posterior aspect of the left base. These appearances could be due to a partial collapse of the left lower lobe and also probably a small effusion.

complication developed, the temperature remained unsettled, and there were occasional spikes to 100° F. for three weeks after admission. Pleural friction was heard at the right base as late as two weeks from admission, but this persisted for only four days X-ray was clear on the 3rd April (Fig. 23). Convalescence was very slow, and the patient lost a good deal



Fig 23 —Case 14 L B

Radiograph 8 weeks later, showing resolution but still slight elevation of the left leaf of the diaphragm.

of weight during the acute stage of illness. Culture of the sputum on admission showed *Staphylococcus pyogenes* as the predominant organism

The picture presented by the above cases conforms to the usual account of influenzal pneumonia. Both cases were examples of staphylococcal infection, but cases of similar type are sometimes encountered among the examples of combined influenza virus and pneumococcal infection Thus, Scadding (1937) described a group

of cases of pneumococcal pneumonia occurring during the 1937 epidemic. In some there were clinical features resembling those given above. It seems probable, therefore, that these cases were infected with influenza virus as well as pneumococci, though direct tests for virus were not made in many instances. Scadding considered that there were clinical differences from ordinary pneumonia, particularly in the general aspect of the patients, the tachypnœa, the irregular pyrexia and the sputum. But he noted the extraordinary variability of the clinical picture, and one patient aged 16, Case 13 in his series, exhibited the picture of fulminating pneumonia, and influenza virus was recovered from the lung at autopsy.

(ii) **Fulminant influenzal pneumonia.** Fulminant influenzal pneumonia is fortunately uncommon. Nevertheless a number of such cases are admitted to hospital in any large town during most influenza epidemics. Moreover, though the condition is commoner in patients over 50, it may occur even in young adults, and it presents a considerable therapeutic problem. As seen during the past four years in Sheffield, the illness is usually insidious for two or more days, and may be thought to be simple influenza. Extreme dyspnœa and prostration then develop without any commensurate pain in the chest to indicate the pulmonary involvement. Within a matter of hours the patient is dangerously ill and presents a shocked appearance, with livid or heliotrope cyanosis, sweating, tachycardia, feeble pulse and a low blood-pressure. The temperature, which may be high initially, falls steadily and may be subnormal at the time of admission to hospital. Cough and sputum may be absent, but in some patients there is a frequent ineffective cough, raising only a little frothy or bloodstained sputum. Physical signs in the chest are those of numerous added sounds, such as râles in all areas. Breath-sounds are weak, but not usually bronchial. Dullness may be absent. As the illness progresses there may be bouts of extreme dyspnœa with great restlessness. The mentality is usually lucid until the end.

The author has seen only two recoveries from an experience of twelve personally witnessed cases, eleven of which were treated with antibiotics in hospital. Case 15 was a typical example of a fatal attack in a previously healthy woman treated only with penicillin. Case 16 was also typical clinically but recovered after treatment with penicillin, terramycin and injections of staphylococcus antitoxin and human influenzal convalescent serum. She developed a spon-

taneous pneumothorax during the acute stage of her illness while i
hospital.

CASE 15. *Fulminant influenzal pneumonia (fatal case).*

Mrs. M. M. U., housewife, aged 36, admitted 26th March 1949 afte
an illness of thirty-six hours' duration She had been nursing her so
from the 21st March, and had not complained of symptoms until 25t

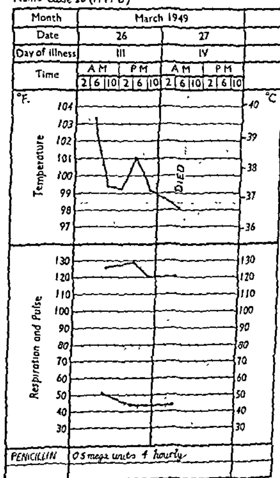


FIG. 24

treatment, and patient died after a bout of extreme dyspnœa twenty hours after admission (Fig. 24)

A limited post-mortem showed large patches of lilac consolidation in right middle and lower lobes, and smaller patches in right upper and left lower lobes These areas showed an organising exudate with poly-

appeared healthy.

Staphylococcus pyogenes was recovered in abundance from both lung and trachea It was sensitive to 0 015 unit per ml. of penicillin. Influenza virus A was recovered from sputum, tracheal mucosa and two different areas of the lung Lung emulsion when diluted to 1 1000 of a 20 per cent suspension w volume was infective for thirteen-day-old fertile eggs

CASE 16 *Fulminant influenzal pneumonia with recovery*

Mrs D H, housewife, aged 38 admitted on 5th February 1951, the sixth day of illness, which began with weakness and a tightness across the front of the chest Three days after the onset there was cough and yellow sputum, running of the eyes and nose, nausea and vomiting Two days before admission there was sudden dyspnœa, she was given sulphonamides On admission temperature was 102 F, pulse 130, respirations 44 (Fig 25) She was extremely dyspnœic and cyanosed, with shallow rattling respirations She could not speak The pharynx was injected and covered with frothy mucus but she could not cough up sputum Blood-pressure was 120 80 on admission, but two hours later was unrecordable, the pulse being 160 She was given 500,000 units of penicillin intramuscularly and 0 5 gram terramycin intravenously When circulatory collapse developed she was given 20,000 units of staphylococcal antitoxin intravenously and later 50 ml of human convalescent influenzal serum X-ray showed patchy shadowing in both right and left lungs (Fig 26) The blood-pressure was recorded as 100 50 at midnight, when the pulse was 156 She was desperately ill for five days, during which she received terramycin both by mouth and intravenously The leucocyte count was 14,000 per cu mm on admission and 23,400 per cu mm. five days later Further injections of serum were given at four-hourly intervals on the first and third hospital day On the fifth hospital day she suddenly became extremely breathless and cyanotic complained of pain in the right chest and had signs of a pneumothorax confirmed by X-ray on this side (Fig 27) On the same day diarrhœa, thought to be due to the terramycin set in and penicillin was therefore substituted Although

taneous pneumothorax during the acute stage of her illness while in hospital.

CASE 15. *Fulminant influenzal pneumonia (fatal case).*

Mrs. M. M. U., housewife, aged 36, admitted 26th March 1949 after an illness of thirty-six hours' duration. She had been nursing her son from the 21st March, and had not complained of symptoms until 25th

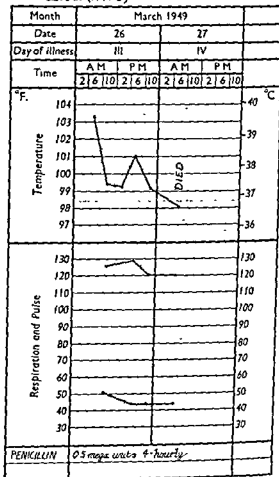


FIG 24

March, when she became breathless and had pain across the lower
She was then seen by Dr Sinclair Evans, who found her very cya
and breathless with a temperature of 105 2° F., pulse 140, blood-pre

100 75. Both bases seemed dull and there were numerous coarse râles. She was given 600,000 units of penicillin in oil and later 1,000,000 units. She was put on oxygen and moved to hospital on 26th March, when the temperature was 103° F., pulse 140 and blood-pressure 70/50. She was pale, with livid cyanosis and dyspnœa with respiration rate of 50. There was occasional dry cough. She was nursed in an oxygen tent and given 00,000 units of penicillin four-hourly. There was no response to eatment, and patient died after a bout of extreme dyspnœa twenty hours ter admission (Fig. 24).

A limited post-mortem showed large patches of lilac consolidation in right middle and lower lobes, and smaller patches in right upper and left lower lobes. These areas showed an organising exudate with poly-morphonuclear leucocytes, much congestion and no actual abscess formation. The tracheal mucosa was reddened, lustreless and presented a wrinkled, corrugated appearance. Histologically there was epithelial necrosis and infiltration of the submucosa with leucocytes. The heart appeared healthy.

Staphylococcus pyogenes was recovered in abundance from both lung and trachea. It was sensitive to 0.015 unit per ml. of penicillin. Influenza virus A was recovered from sputum, tracheal mucosa and two different areas of the lung. Lung emulsion when diluted to 1 : 1000 of a 20 per cent suspension w/volume was infective for thirteen-day-old fertile eggs.

Case 16. *Fulminant influenzal pneumonia with recovery*

Mrs. D. H., housewife aged 38, admitted on 5th February 1951, the sixth day of illness, which began with weakness and a tightness across the front of the chest. Three days after the onset there was cough and yellow sputum, running of the eyes and nose, nausea and vomiting. Two days before admission there was sudden dyspnœa. She was given sulphona-mides. On admission temperature was 102° F., pulse 130, respirations 44 (Fig. 25). She was extremely dyspnœic and cyanosed with shallow rattling respirations. She could not speak. The pharynx was injected and covered with frothy mucus but she could not cough up sputum. Blood-pressure was 120/80 on admission but two hours later was un-recordable, the pulse being 160. She was given 500,000 units of penicillin intramuscularly and 0.5 gram terramycin intravenously. When circu-latory collapse developed she was given 20,000 units of staphylococcal antitoxin intravenously and later 50 ml. of human convalescent influenzal serum. X-ray showed patchy shadowing in both right and left lungs (Fig. 26). The blood pressure was recorded as 100/80 at midnight, when the pulse was 156. She was desperately ill for five days, during which she received terramycin both by mouth and intravenously. The leucocyte count was 14,000 per cu. mm. on admission and 21,400 per cu. mm. five days later. Further injections of serum were given at four-hourly intervals on the first and third hospital day. On the fifth hospital day she suddenly became extremely breathless and cyanotic, complained of pain in the right chest and had signs of a pneumothorax, confirmed by X-ray on this side (Fig. 27). On the same day diarrhœa, thought to be due to the terramycin, set in, and penicillin was therefore substituted. Although

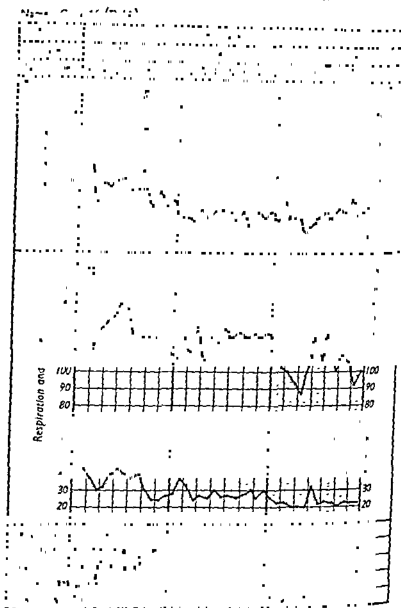


Fig 25

Fig 26 — Radiograph on the 6th day of illness, showing bilateral mottled opacities.

Fig 27 — Radiograph on the 14th day of illness There is a pneumothorax on the right side with partial collapse of the right lung The left lung still shows some mottling

readmitted with renewed cough and sputum four days later. Good response to further penicillin . . .
recovered The . . .
patient had a past
before and had in

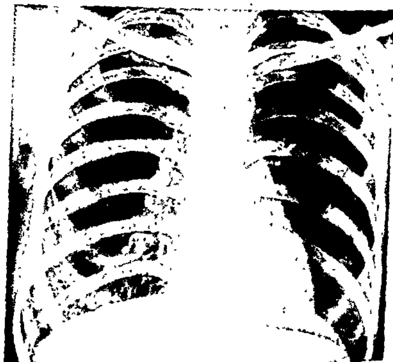


FIG 28 —Case 16 D H.
Radiograph 3 months later, showing a normal appearance.

admission She had had occasional attacks of bronchitis in the past The sputum yielded *Staphylococcus pyogenes* in enormous numbers on admission The organism was sensitive to 0 125 unit of penicillin per ml and 1 5 micrograms per ml of aureomycin. Influenza virus A was also recovered from the sputum obtained on admission and which was inoculated into fertile hens' eggs

The particular clinical picture afforded by these cases is apparently invariably associated with both *Staphylococcus pyogenes* and influenza virus infection Either influenza virus A or virus B may be found

The staphylococci are present usually in enormous numbers in the sputum and may form actual colonies in the lung. They may grow as dense masses on the necrotic surface of the trachea or bronchi. The cellular reaction of these epithelia is one of necrosis down to the basal layer of the mucosa, or even as far as the muscularis mucosæ. In some instances necrosis may involve the entire bronchiole, but it seems likely that this is caused by thrombosis of arterial branches. The cellular reaction in the lungs is variable. Sometimes there is no leucocytic reaction, but only œdema, hæmorrhage and masses of organisms. In other cases well-defined leucocytic infiltration and even abscess formation occurs.

The detailed histological findings in cases of pneumonia during the 1918 epidemic described by Winternitz *et al.* (1920) appear to resemble that found in these more recent cases of fulminant staphylococcal pneumonia. The difference from 1918 is that in the latter epidemic no constant bacterial flora was encountered, whereas the *Staphylococcus pyogenes* seems to be the only organism reported in modern times in fulminating cases.

The manner in which the staphylococcus and the influenza virus potentiate each other's attack is far from clear. The enormous pullulation of staphylococci and the considerable quantities of influenza virus detected in the lung do in fact suggest a synergism. It is also difficult to allocate responsibility for the various clinical phenomena to one or other agent. Nevertheless, the relatively disappointing response to antibiotics compared with that of other forms of pneumonia may be an indication that the virus has a definite rôle in the production either of the cellular necrosis or of the general toxæmia. More cannot be said at the present time.

(iii) **Post-influenzal and other varieties of pneumonia encountered during influenza epidemics.** Most patients with consolidation of the lungs encountered in hospital practice during the epidemics of the last few years were not recognisably different clinically from cases occurring quite apart from influenza. In the clinical sense, therefore, there was little justification for use of the term influenzal pneumonia as a description of these cases. Yet about 50 per cent of all cases of consolidation occurring during the period of prevalence of epidemic influenza yield serological if not actual cultural evidence of virus infection. This figure exceeds that for the combined subclinical and clinical infections with virus in the community (Chapter 2, page 101) and must indicate a relationship between pneumonia and influenza virus infection.

The cases of consolidation encountered in Sheffield during the influenza epidemics of 1949 and 1951 constituted a heterogeneous group. Tests of garglings, sputa and of sera enabled a precise identification of those patients who had either been infected with virus before onset of their lung complication or who developed the infection synchronously with the pneumonia (Table 3). Moreover, the majority of these patients were examined by bacteriological culture of the sputum, and mice were inoculated intraperitoneally in the search for pneumococci.

The results of the bacteriological work indicated the predominance of the pneumococcus as the chief bacterial agent concerned in these pneumonias. The *Staphylococcus pyogenes* easily took second place to the pneumococci, and a minority of patients yielded either no pathogenic organism in the sputum, or else *Hæmophilus influenzæ* or a hæmolytic streptococcus. Enough has been said concerning the staphylococcus to indicate the character of the clinical picture in this infection. The pneumococcal pneumonias presented, however, a much greater clinical variation. It is possible by measurement of the antibody levels against the virus to distinguish a pneumococcal infection occurring synchronously with the virus infection from that in an important group of cases which develop the bacterial complication some days or even weeks after the virus infection. The latter condition of post-influenzal pneumonia was recognised years before the recent work on the virus infection. Lichtenstern (1905) speaks of pneumonia following an attack of influenza in these terms: 'One, two, or even more days later, a relapse occurs sometimes but not always with a rigor; the influenza manifestations seem to recrudesce, but in reality they are the first signs of the slowly developing pneumonia. . . . In these cases the pneumonia attack comes on the first time the influenza convalescent goes out, hence the universal view that the patient convalescing from influenza is very liable to catch cold, and easily gets inflammation of the lungs.'

An analysis of 62 tested cases of pneumonia associated with influenza and collected from the influenza epidemics in 1949 and 1951 in Sheffield is given in Table 3. Forty-one cases were judged to be synchronous virus and bacterial infections and 21 were post-influenzal. Ten patients died. There was an equal number of the two sexes, and the age-distribution indicated a preponderance of those over the age of 40. Twenty-three pneumonias were classified as broncho-pneumonic in type and, of these, 12 were associated with the staphylococcus. Thirty-four were lobar and 5 were

segmental pneumonias in whom the consolidation affected only a portion of a lobe. A considerable number of those over the age of 40 gave a history suggesting previous chronic bronchitis or some other

TABLE 3

Pneumonia during an Influenza Epidemic
(Sheffield, 1949 and 1951)

	No.	Sex		Ages			Broncho-pneumonia	Lobar pneumonia	Segmental pneumonia
		Males	Females	< 40	40–60	Over 60			
Synchronous with influenza	41	30	11	10	16	15	22	12	3
Post-influenzal	11	9	[illegible]	4	2	[illegible]	[illegible]	[illegible]	2
Total	52	[illegible]	[illegible]	14	[illegible]	[illegible]	[illegible]	14	5

espiratory tract disease, such as an attack of previous pneumonia. Three patients had established bronchiectasis prior to their attack of influenza.

It is not possible to give a detailed account of the clinical features in these patients which would cover their varying histories and manifestations. Some illnesses were severe, many were mild. Most patients had symptoms of a cold, or cough, or of headache, and muscular aching for a few days before the onset of dyspnœa, sudden pain in the chest and expectoration which indicated the chest complication. Though the majority of patients were febrile on admission, a good therapeutic response was obtained with antibiotics or with sulphonamides, and the temperature, pulse and respiration usually settled rapidly. The physical signs, however, persisted, as is usual with cases of pneumonia treated with chemotherapeutic agents. There was usually no difficulty in deciding that lung consolidation was present because of the combination of dullness, bronchial breathing and crackling râles. Added sounds were, however, heard in other areas as well, though not so diffusely as in the cases of staphylococcal pneumonia. The leucocyte count varied greatly, being barely raised in some or showing a leucocytosis of 20,000 or more per cu. mm. Complications were unusual in these patients, and the duration of illness was often related to the age of the patient rather than to the extent of consolidation. Some of the patients in the younger age groups were however severely ill, and in these two or more lobes were consolidated.

There were no sharp clinical differences between the synchronous

The cases of consolidation encountered in Sheffield during the influenza epidemics of 1949 and 1951 constituted a *heterogeneous* group. Tests of garglings, sputa and of sera enabled a precise identification of those patients who had either been infected with virus before onset of their lung complication or who developed the infection synchronously with the pneumonia (Table 3). Moreover, the majority of these patients were examined by bacteriological culture of the sputum, and mice were inoculated intraperitoneally in the search for pneumococci.

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Synchronous with influenza	41	20	21	10	16	15	19	19	3
Post influenzal	21	9	12	4	9	8	4	15	2
Total	62	29	33	14	25	23	23	34	5

respiratory tract disease, such as an attack of previous pneumonia. Three patients had established bronchiectasis prior to their attack of influenza.

It is not possible to give a detailed account of the clinical features in these patients which would cover their varying histories and manifestations. Some illnesses were severe, many were mild. Most patients had symptoms of a cold, or cough, or of headache, and muscular aching for a few days before the onset of dyspnœa, sudden pain in the chest and expectoration which indicated the chest complication. Though the majority of patients were febrile on admission, a good therapeutic response was obtained with antibiotics or with sulphonamides, and the temperature, pulse and respiration usually settled rapidly. The physical signs, however, persisted, as is usual with cases of pneumonia treated with chemotherapeutic agents. There was usually no difficulty in deciding that lung consolidation was present because of the combination of dullness, bronchial breathing and crackling râles. Added sounds were, however, heard in other areas as well, though not so diffusely as in the cases of staphylococcal pneumonia. The leucocyte count varied greatly, being barely raised in some or showing a leucocytosis of 20,000 or more per cu. mm. Complications were unusual in these patients, and the duration of illness was often related to the age of the patient rather than to the extent of consolidation. Some of the patients in the younger age-groups were, however, severely ill, and in these two or more lobes were consolidated.

There were no sharp clinical differences between the synchronous

The cases of consolidation encountered in Sheffield during the influenza epidemics of 1949 and 1951 constituted a heterogeneous group. Tests of garglings, sputa and of sera enabled a precise identification of those patients who had either been infected with virus before onset of their lung complication or who developed the infection synchronously with the pneumonia (Table 3). Moreover the majority of these patients were examined by bacteriological culture of the sputum, and mice were inoculated intraperitoneally in the search for pneumococci

The results of the bacteriological work indicated the predominance of the pneumococcus as the chief bacterial agent concerned in these pneumonias. The *Staphylococcus pyogenes* easily took second place to the pneumococci, and a minority of patients yielded either no pathogenic organism in the sputum, or else *Hæmophilus influenzæ* or a hæmolytic streptococcus. Enough has been said concerning the staphylococcus to indicate the character of the clinical picture in this infection. The pneumococcal pneumonias presented, however, a much greater clinical variation. It is possible by measurement of the antibody levels against the virus to distinguish a pneumococcal infection occurring synchronously with the virus infection from that in an important group of cases which develop the bacterial complication some days or even weeks after the virus infection. The latter condition of post-influenzal pneumonia was recognised years before the recent work on the virus infection. Lichtenstern (1905) speaks of pneumonia following an attack of influenza in these terms: 'One, two, or even more days later, a relapse occurs sometimes but not always with a rigor; the influenza manifestations seem to recrudesce, but in reality they are the first signs of the slowly developing pneumonia. . In these cases the pneumonia attack comes on the first time the influenza convalescent goes out, hence the universal view that the patient convalescing from influenza is very liable to catch cold, and easily gets inflammation of the lungs'

An analysis of 62 tested cases of pneumonia associated with influenza and collected from the influenza epidemics in 1949 and 1951 in Sheffield is given in Table 3 Forty-one cases were judged to be synchronous virus and bacterial infections and 21 were post-influenzal. Ten patients died. There was an equal number of the two sexes, and the age-distribution indicated a preponderance of those over the age of 40 Twenty-three pneumonias were classified as broncho-pneumonic in type and, of these, 12 were associated with the staphylococcus. Thirty-four were lobar and 5 were

egmental pneumonias in whom the consolidation affected only a
ortion of a lobe A considerable number of those over the age of
gave a history suggesting previous chronic bronchitis or some other

TABLE 3

Pneumonia during an Influenza Epidemic
(Sheffield, 1949 and 1951)

	No	Sex		Ages			Broncho pneumonia	Lobar pneumonia	Segmental pneumonia
		Males	Females	<40	40-60	Over 60			
Synchronous with influenza	41	20	21	10	16	15	19	19	3
Post influenzal	21	9	12	4	9	8	4	15	2
Total	62	29	33	14	25	23	23	34	5

respiratory tract disease, such as an attack of previous pneumonia
Three patients had established bronchiectasis prior to their attack of
influenza

It is not possible to give a detailed account of the clinical features
in these patients which would cover their varying histories and
manifestations Some illnesses were severe, many were mild Most
patients had symptoms of a cold, or cough, or of headache, and mus-
cular aching for a few days before the onset of dyspnœa, sudden pain in
the chest and expectoration which indicated the chest complication
Though the majority of patients were febrile on admission, a good
therapeutic response was obtained with antibiotics or with sul-
phonamides, and the temperature, pulse and respiration usually
settled rapidly The physical signs, however, persisted, as is
usual with cases of pneumonia treated with chemotherapeutic
agents There was usually no difficulty in deciding that lung
onsolidation was present because of the combination of dullness,
ronchial breathing and crackling râles Added sounds were,
however, heard in other areas as well, though not so diffusely as in
the cases of staphylococcal pneumonia The leucocyte count varied
greatly, being barely raised in some or showing a leucocytosis of
20,000 or more per cu mm Complications were unusual in these
atients, and the duration of illness was often related to the age of
e patient rather than to the extent of consolidation Some of the
tients in the younger age-groups were, however, severely ill, and
hese two or more lobes were consolidated
here were no sharp clinical differences between the synchron-

and the post-influenzal cases; nor could the patients with scattered broncho-pneumonic involvement be differentiated clearly from those with lobar distribution. These cases of pneumococcal pneumonia could not be distinguished clinically from ordinary pneumococcal pneumonia unassociated with influenza. A detailed investigation



FIG 29—Case 17 A M F Pneumococcal pneumonia in a bronchiectatic subject

Radiograph on the 5th day of illness, showing opacity at the left base and a mottled, honeycomb-like appearance at the right base.

made by Tyrrell (1952) should be consulted by those interested Two cases may serve to illustrate these two varieties of pneumonia occurring during an influenza epidemic.

CASE 17 *Pneumococcal pneumonia in a woman with bronchiectasis.*

Mrs. A. M F, aged 40, housewife, admitted 5th February 1951. She had had a cough for twenty years, and four separate attacks of pneumonia. Her husband became ill with influenza on the 31st January, and on the 1st February she shivered, developed a headache, sore eyes and weakness. During the next few days she had increased cough and sputum amounting

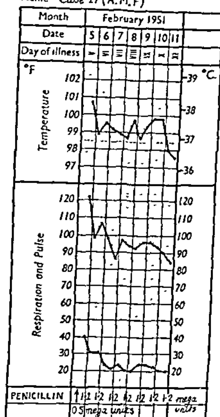


FIG 31

CASE 18. *Post-influenzal pneumococcal pneumonia.*

G B , aged 47, file-cutter, began to have a cold, feverishness and aching on the 1st February 1951 He was in bed for three days One week later he was better, and returned to work. On the next day he was shivering again, and a day later developed a cough and yellow brown-streaked

râles and greatly diminished breath-sounds. X-ray showed uniform opacity suggesting partial consolidation of the right upper lobe and apex of the right lower lobe. The leucocyte count was 8,500 per cu. mm. The sputum yielded a pneumococcus type III The serum titre for influenza A soluble antigen by the complement-fixation test was 32 and ten days later 48 These titres are indicative of recent infection by

influenza virus A The course in this patient was one of rapid recovery with radiological resolution by the 27th February.

Finally, an important small group of patients admitted to hospital with every indication of a developing lung consolidation showed rapid improvement and exhibited clear X-ray skiagrams of the lung-fields Such patients were also encountered in 1937, and then grouped as examples of abortive pneumonia This title might indicate a trifling condition, but in fact many patients were critically ill, but improved rapidly without ever developing pulmonary consolidation As this picture is relatively common, and must be differentiated from either ordinary influenzal pneumonia or bronchiolitis, an illustrative case will be described

CASE 19 *Abortive pneumonia*

Mrs D G, aged 52, housewife, developed an attack of influenza at the same time as her husband, and after some days of illness took to bed because of pain in the left side of the chest She was delirious on admission to hospital on the next day, 17th April 1949 The temperature was 103 4° F, pulse 110, respirations 30 (Fig 32) Respirations were shallow She complained of a choking sensation in the throat, which showed only yellow, bloodstained sputum on the posterior pharyngeal wall The chest showed an impaired percussion note and localised bronchial breathing at the left base Radiologically the X-ray was normal on the next day, when she had improved, but was still coughing and complaining of the throat Treatment with penicillin was instituted on admission Sputum culture yielded only *M catarrhalis* The leucocyte count was 5,000 and later 11,000 per cu mm. The serum titre for influenza A increased thirty-two times by the complement-fixation test and eight times by the agglutination-inhibition test as the patient entered convalescence thus indicating recent infection by influenza virus A

FIG 32

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CHAPTER 4

PATHOLOGY OF INFLUENZA

Influenza virus infection in animals

THE mechanism of influenza in man can best be visualised by an understanding of the process of infection induced by influenza virus in experimental animals. Beginning with the virus as it is present in garglings or sputum from cases of human influenza, it is only possible to transmit the infection to a limited range of animal hosts. In fact, as is obvious from the history of negative attempts to transmit influenza from man to animals, only the ferret and the fertile hen's egg furnish suitable susceptible animal hosts. However, influenza virus A induces in the ferret a short febrile illness remarkably similar in many ways to the human disease.

Forty-eight hours after the intranasal instillation of garglings into a ferret, the animal becomes quiet and listless, the temperature rises sharply to between 104° and 105° F., the nose becomes moist, and food is refused. Fever lasts for three days, with a drop to normal on the second day and a renewed rise of temperature on the third day. As the illness progresses, sneezing attacks may develop, accompanied by a purulent discharge from the nose. As soon as the temperature is normal, the animal becomes more lively, and soon recovers. Weight is lost, however, and it may be a week or more before normal condition is restored.

If the ferret is inoculated with virus intranasally under an anæsthetic such as ether, no lung lesions develop unless the virus has been modified by repeated transfer from one ferret to another. Such 'adapted' virus, as it is called, will often induce fever after an incubation period of twenty-four or thirty-six hours, and as fever progresses, the respirations may become more laboured and thumping than in the normal ferret. When sacrificed at any stage from the fourth day after inoculation, such animals exhibit lesions visible to the naked eye in the form of purplish-brown areas located chiefly near the hila of the lung, but often spreading along a lung segment or even involving an entire lobe. Only exceptionally virulent strains of influenza virus A, such as have been passaged 100 or more times through the ferret, will actually kill the animal. Such ferrets exhibit a consolidation of three-quarters or more of the lungs at the time of death, which may not occur until a week or ten days after in-

To complete the picture of influenza in the ferret, it is necessary to indicate that after inoculation intranasally the virus reaches its highest titre in the mucosa of the nasal turbinates, but that some virus is also present in the lungs, particularly if the animal is inoculated under an anæsthetic. Moreover, virus is present in the lungs when there are no visible macroscopic lesions. Although strains of influenza virus A will regularly infect the ferret either directly or occasionally only after passage through eggs, influenza virus B strains usually fail to produce any symptoms or lesions. Nevertheless, infection does occur in such animals after inoculation with influenza virus B, for the ferret's serum develops antibodies specific for the virus used originally and in greater concentration than that which would be found after intranasal inoculation with non-infective virus. A much-passaged strain of influenza B occasionally does induce a mild fever in the ferret, but the illness is trivial and the nasal mucosa may remain normal.

Recovery of the ferret from infection by influenza virus is thus accompanied by the formation of antibodies specifically neutralizing the infecting virus. At the same time, resistance develops to a second intranasal inoculation with the same or serologically related strains of virus. This immunity, which is at its height in early convalescence, is short-lived, and three to six months after inoculation, reinoculation with virus will again induce fever and nasal symptoms. The illness is then usually milder than the first attack, and even if anæsthesia is employed and the strain of virus is capable of inducing lung lesions, no lesions in fact do develop in the lungs of such reinoculated ferrets. The state of waned immunity is thus clearly distinct from that of primary susceptibility. In an animal without previous contact with influenza virus, an injection of live virus subcutaneously or intraperitoneally completely fails to induce any symptoms or signs of infection. Antibodies develop in the serum, however, but a full degree of immunity to subsequent intranasal inoculation cannot be obtained. Fever and nasal symptoms develop after intranasal 'challenge', though the attack may be milder than in unimmunized animals. If a parenteral inoculation is given to animals with waned immunity either with living or *formolised* (inactivated) virus, a full degree of immunity is restored and antibodies rise to a high titre in the serum. Such immunity is again species-specific. There is no demonstrable cross-immunity between influenza viruses A and B, after recovery from infection or after immunization by parenteral injection. Cross-protection between different strains of influenza A and between influenza virus A

and the serologically related swine influenza virus is, however, exhibited.

Influenza virus is nowadays more conveniently cultivated directly from human secretions by the injection of these materials into fertile hens' eggs. In this species also the virus has to be introduced into the new host by a particular route The amniotic cavity surrounding the growing embryo contains normally a small amount of fluid, and as the beak projects into this amniotic fluid, it is obvious that materials injected into the amniotic cavity can thus obtain entry into the respiratory tract of the embryo In fact, it has been found that human influenza virus, as it exists in secretions obtained from man, will only infect the chick embryo at all regularly if introduced into the amniotic sac Susceptibility of the embryo is greatest at about the thirteenth day of development, at a time when the lung is beginning to form its primitive bronchiolar epithelium. Virus

inoculate, and a relatively large yield of cell-free fluid containing a high titre of virus can be obtained forty-eight hours after allantoic inoculation of ten- or eleven-day-old embryos with influenza virus strains previously passed by the amniotic route

Again, as in the case of the ferret, influenza virus B is more difficult to cultivate in the chick than is influenza virus A. Amniotic inoculation may succeed, however, even if the garglings are non-infective for the ferret The chick lung is the best source of virus after amniotic inoculation at the thirteenth day of embryonic development, but once the virus has become adapted to the chick, the allantoic cavity will also support its growth

The mouse is not fully susceptible either to human influenza viruses A or B as they exist in human secretions and cannot be relied upon for primary isolation of virus from human garglings Passage either in the ferret or in eggs modifies the virus, however, and inoculation of mice intranasally with either ferret- or egg-infected material may result in infection Usually several transfers are required in mice by the intranasal route under ether anæsthesia, before the infection is accompanied by the development of lung lesions The lesions in the mouse resemble those found in ferrets

passaged repeatedly in mice soon become virulent, and kill regularly in four to ten days, even if the inoculating emulsions made from the infected lungs are diluted a thousand-fold or more Death occurs from the fourth day onwards, and the mouse shows three-quarters or

FIGS 33-40 —Histological changes in the nasal turbinates of the ferret during influenza virus A infection



FIG 33



FIG 34

Fig 33 —Horizontal section of turbinate system of normal ferret Anterior turbinates form complicated whorl covered by respiratory epithelium (L P)

Fig 34 —High-power of Fig 33 Ciliated columnar epithelium covering anterior turbinates of normal ferret.

total lung consolidation The virus does not grow in the mouse's nasal cavity, as it does in the ferret, though it can be found in the tracheal mucosa and fluid Probably because of this, influenza in the mouse is normally not contagious, whereas the ferret can be infected simply by contact with another infected ferret or by inhaling air containing infected droplets Mice cannot normally be infected unless an anæsthetic is used during the inoculation, but if they are exposed to air containing atomised droplets obtained by bubbling air through a fluid suspension of virus, consolidation of the lungs develops Presumably, therefore, deep penetration of droplets into

the lungs is needed to initiate infection, and the function of anæsthesia is simply to permit aspiration past the normal reflex barriers of the nose and larynx. Influenzal infection in mice which is insufficiently severe to kill is accompanied by the development of immunity to reinoculation. Or, as in the case of the ferret, immunity can be produced by parenteral inoculation either subcutaneously or



FIG. 35 FIG. 36

FIG. 35.—Turbinates 48 hours after infection with influenza virus A (PR8 strain) (L. P.)
Epithelial necrosis and formation of a cellular exudate in the air-passages.
FIG. 36.—High-power of Fig. 35.
The ciliated columnar epithelium has been destroyed. There is a simple basal layer of cells covering the submucosa. The air-passages contain desquamated cells, red cells, leucocytes, mucus and debris.

intraperitoneally. Live or inactivated virus can be used, and the degree of immunity is such that challenge by intranasal inoculation under anæsthesia fails to cause lung lesions. But the immunity is type-specific, and influenza virus A will not immunize against influenza virus B or vice versa.

Histology of experimental influenza in animals

(a) *Nasal lesions.* The ferret is the most suitable animal in which to study the essential lesion of influenza virus infection. The nasal

cartilages of this animal form a complicated whorl coated by a thin epithelium of ciliated columnar cells based upon a primitive basal layer and a vascular submucosa (Figs. 33 and 34). Forty-eight hours after intranasal inoculation of virus-containing fluid ...



FIG 37 FIG 38

FIG 37 —Regenerating epithelium on the 6th day after infection. The cells form a stratified epithelium three layers deep covering an engorged submucosa The air-passages still contain a richly cellular exudate.
FIG 38 —High-power of Fig 37 to show the stratified columnar epithelium

an exudate composed of leucocytes, necrotic debris and muc collects in the air-passages (Figs 35 and 36) The mucosal ep thelium is then stripped to the basal layer, and in the next few da active mitosis occurs in this layer, so that a stratified barrier of cel re-forms By about the sixth or eighth day the epithelium is seven cells deep, but is not yet ciliated (Figs 37 and 38) About fourtee to twenty days after the onset of infection the nasal epithelium i fully restored to normal, and is then indistinguishable from a norma

([illegible]). It is at this stage that re-inoculation of

based upon a lesion of the finest bronchioles essentially similar to

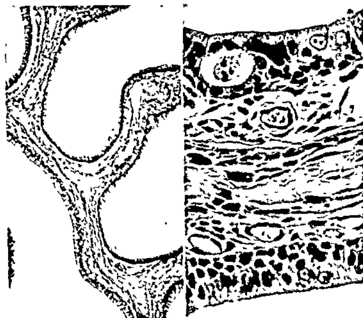


Fig. 39 — Normal mucosa regenerated 14 days after infection
Numerous goblet cells are present

Fig. 40 — High-power of Fig. 39
The epithelium is just beginning to sprout cilia

that found in the nose of the infected ferret. The earliest lesion is a necrosis of the ciliated epithelium normally present in such bronchioles (Figs. 41 and 42), with resultant formation of an exudate in the lumen and a stripping of the epithelium to a basal layer (Figs. 43 and 44). The alveoli adjoining infected bronchioles may show some atelectasis, perhaps because of blocking of the bronchiole by secretion, and there may also be some œdema and congestion. The

larger bronchioles and bronchi are not significantly abnormal, and there is no real alveolar exudate such as is found in pneumonic consolidation. The bronchiolar lesion is repaired by a process of cell division analogous to that observed in the nasal mucosa, but there may be more widespread œdema and cellular infiltration around the

FIGS. 41–50.—Histological changes in the lung of the ferret during influenza virus A infection.



FIG. 41 FIG. 42

FIG. 41.—Normal ferret lung showing alveoli and bronchioles. (L.P.)
FIG. 42.—High-power of FIG. 41.
The bronchiolar epithelium is composed of ciliated columnar cells.

bronchiole at this stage (Figs. 45 and 46). In ferrets which succumb to infection the alveoli are occupied by œdema fluid and hæmorrhage in which scanty cells of a mononuclear variety are seen. Again, however, there is intensive destruction of the bronchioles from which the lesion radiates out (Figs. 47 and 48). Repair of the bronchiole (Figs. 49 and 50) is a more complex process than repair of turbinate epithelium, and alveoli may appear to be lined by cells of an elongated or stratified character for some days, or even weeks, after the initial lesion (Straub, 1937).

There does not appear to be any essential difference between the lung lesions of infected ferrets and mice.

(c) *Lesions in the chick embryo* These are of less interest from the standpoint of human pathology. Nevertheless, the fact that infection causes the epithelium of the primitive bronchioles of the embryo lung to undergo complete necrosis and that an exudate of debris and isintegrated cells collects in the spaces formed by these bronchioles a striking testimony to the cell-tropism of the influenza virus. estruction of the embryo lung is accompanied by a good deal of



Fig 43 Fig 44

Fig 43 Ferret lung 4 days after infection with influenza virus A (PR8 strain) showing a focus of bronchiolitis and alveolar œdema in the peribronchial zone (L P)

Fig 44 High-power of Fig 43 showing wall of bronchiole The epithelium has been destroyed and an exudate of desquamated cells polymorphs and debris coats the lining of basal cells Adjacent alveoli show interstitial infiltration of the alveoli wall and œdema

shrinkage and apparent 'consolidation' from filling up of the 'alveoli' The trachea of the chick embryo contains necrotic cells and leucocytes with a bizarre appearance, and this cellular picture was formerly used as a diagnostic indication of the lung infection by the virus (Burnet, 1940) The affected embryo has a stunted appearance if taken out three or four days after amniotic inoculation, and is frequently killed by the infection, presumably because of dispersal of the virus from the lung to more vital cells. The infection thus becomes generalised throughout the embryo, a state of affairs

contrasting with the infection of the ferret or mouse in which the virus does not involve tissues outside the respiratory tract.

Hens' eggs can also be infected by the allantoic route with strains of influenza virus previously passaged amniotically or in ferrets or mice, and then the virus may not attack the embryo significantly, so that specific lesions are not observed The allantoic cells undergo disintegration. Inoculation of passaged virus on the external membrane



Fig 45 Fig 46

Fig 45 —Ferret lung 6 days after infection showing an area of consolidation

Two bronchioles with regenerating epithelium and mucus plugs are surrounded by an area of cellular infiltration of the alveolar walls and alveoli

(the chorio-allantoic membrane) can also result in infection of the cells of the latter, with the production of necrosis and some hyperplasia But such allantoic and chorio-allantoic membrane infections are highly artificial, and bear little if any analogy to human pathology.

Influenza virus infection in man

The exact mode of transference of infection from man to man is unknown, but is presumed to be by the inhalation of infected droplets

discharged into the air during the process of talking, coughing and sneezing. No one doubts that influenza is a contagious disease, and it seems reasonable that the larger particles with a short trajectory, such as are discharged and inhaled during close contact, are more important than the minute airborne particles which can remain suspended in the air for a long period of time. It cannot, however, be denied that such minute particles can carry infection indirectly

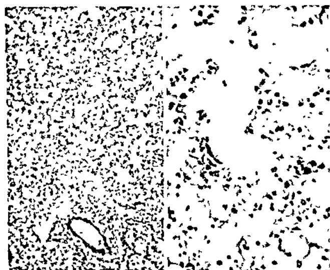


FIG 47 FIG 48

Fig 47 – Ferret lung 6 days after infection with PRS virus. The inoculum was more concentrated than that used in the ferrets shown in Figs 43 to 46. The animal died on the 6th day, the lungs [illegible] h-power view [illegible] œdema and [illegible] infiltration is scanty

from one host to another, or that dust containing dried particles of sputum or naso-pharyngeal secretion may also contain viable particles of influenza. Experimental inoculation of human volunteers is more successful in producing infection if aspiration of atomised droplets is practised rather than simple nasal instillation (Henle and others, 1946).

The incubation period can rarely be estimated in natural infection. In those instances where a relatively isolated community appears to

have been infected from a single source, it is likely that forty-eight hours or more elapse from the time of contact to the development of symptoms. In a family, however, symptoms appear in the various members within shorter periods than forty-eight hours Moreover, after artificial infection of volunteers with atomised virus, the incubation period may be as short as *twenty-four hours* There seems no inherent reason why the virus may not gain entrance to a

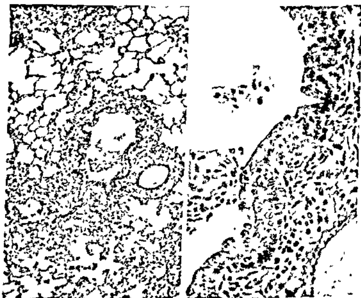


FIG 49 FIG 50

FIG 49 —Ferret lung 7 days after infection, showing a more circumscribed area of peribronchial infiltration surrounding an affected bronchiole

FIG. 50 —*High-power of* FIG 49
The bronchiolar epithelium has a stratified appearance

host, and perhaps to all membe ely and
remain latent. Symptoms may
tion of virus, if some environmen
disturbs the natural resistance of the respiratory tract, as in the case of swine influenza This would explain the instances of apparent simultaneous involvement of all members of a family. Also during explosive outbreaks in schools or other communities it is difficult to account for the extremely rapid build-up of infection, except by some sort of mechanism as that outlined

The virus is present in the nasal and faucial secretions at the earliest

phase of the clinical illness. It persists probably until the fever subsides, but the best time to recover virus is before rather than at the peak of illness. This may be because a rapid development of a low concentration of antibodies in the region of the lesions causes the virus to be partially neutralized, and thereby hinders it from developing when it is inoculated into laboratory animals. Serum antibody levels begin to rise on about the fifth day of illness and reach a peak at the eighth to the fourteenth day. The titres then begin to subside, though they do not return to pre-infection levels for some months. In actual fact the period of duration of the elevation in titre of antibodies varies according to the type of antibodies concerned. Antibody capable of neutralizing the virus, and therefore of preventing its multiplication *in vivo*, is relatively more permanent than that capable of fixing complement in the presence of the so-called soluble antigen of the virus. Antibodies demonstrated by the agglutination-inhibition test *in vitro* resemble those demonstrated by the neutralization test *in vivo*, and are thus more long-lasting in the serum than the complement-fixing antibody. In effect, neutralizing and inhibiting antibodies remain demonstrable for at least six months after infection, but are then at a lower concentration than that found during the phase of convalescence. Complement-fixing antibodies to the soluble antigen disappear in a matter of a few weeks after infection. The antibody response in man appears to be as vigorous after a subclinical as after an overt infection. However, the antibody titre found in convalescence from influenza accompanied by pneumonia is often impressively high and perhaps suggests a more prolonged stimulation of the immune mechanism in such cases. The subject of immunity is dealt with in Chapters 6 and 13.

Histology of influenza in man

There is no exact knowledge concerning the specific lesions of influenza virus in man. So far as the nose is concerned, there is a probability that some actual inflammatory process is in progress during influenza, because the nose is frequently stuffy or actually blocked. But there is no evidence on which to base a description of the cytological picture. Smears taken from the tonsils and fauces during the early phase of uncomplicated influenza usually show collections of squamous cells and occasionally smaller rounded cells, but no firm diagnostic significance can be attached to this picture.

The only lesions found in man which bear any resemblance to the lesions described above in animals are those found in cases of

have been infected from a single source, it is likely that forty-eight hours or more elapse from the time of contact to the development of symptoms. In a family, however, symptoms appear in the various members within shorter periods than forty-eight hours. Moreover, after artificial infection of volunteers with atomised virus, the incubation period may be as short as twenty-four hours. There seems no inherent reason why the virus may not gain entrance to a



FIG 49 FIG. 50

FIG 49 —Ferret lung 7 days after infection, showing a more circumscribed area of peribronchial infiltration surrounding an affected bronchiole

FIG 50 —High-power of FIG 49
The bronchiolar epithelium has a stratified appearance

host, and perhaps to all members of a family simultaneously and remain latent. Symptoms may then arise as a result of multiplication of virus, if some environmental change such as sudden chilling disturbs the natural resistance of the respiratory tract, as in the case of swine influenza. This would explain the instances of apparent simultaneous involvement of all members of a family. Also during explosive outbreaks in schools or other communities it is difficult to account for the extremely rapid build-up of infection, except by some sort of mechanism as that outlined.

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fulminant staphylococcal pneumonia. As has been pointed out in Chapter 3, these cases represent a combined infection with either influenza virus A or B and the *Staphylococcus pyogenes* Accordingly, it is difficult or impossible to allocate responsibility for the particular lesions either to the virus or to the staphylococcus A reasonable view would be that the virus induces the surface lesions

FIGS. 51–62 —Histology of influenzal pneumonia in man



FIG 51 FIG 52

Fig 51 —Trachea from a patient with fatal broncho-pneumonia unassociated with influenza virus infection (L P)
The epithelium of columnar ciliated cells is normal in structure The submucosa is wide and apart from an increase in mononuclear cells is normal in structure
Fig 52 —High-power view of Fig 51.
Normal tracheal epithelium with columnar ciliated cells

of the trachea and bronchioles, and that the staphylococcus finds the resultant necrotic material to be a good culture medium. But another view which cannot be refuted is that the staphylococcus alone is responsible for the lesions which result from the local effect of exotoxins of the cocci It is not easy to decide between the merits of these two interpretations, and it is only possible to describe and illustrate the lesions which are found at autopsy.

The trachea exhibits naked-eye congestion and a wrinkled, pitted appearance. The lung is intensely congested, and may show either no focal lesions or else there may be visible purple areas of consolidation in several different areas. If death does not result for some days, abscesses of various sizes may be found on section of such consolidated areas. In any case there is intense œdema, and the consolidated lung literally pours out fluid from the cut surface.

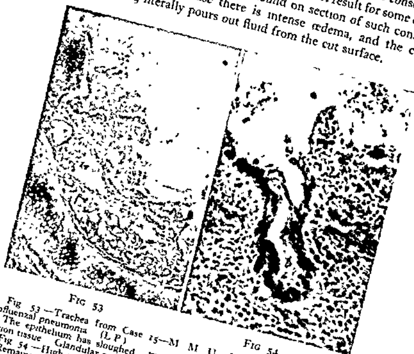


FIG 53

FIG 54

Fig 53.—Trachea from Case 15—M M U Fulminant staphylococcal influenzal pneumonia (L P)

The epithelium has sloughed. The submucosa is converted into granulation tissue. Glandular remnants are seen in the submucosa.

Fig 54.—High-power view of Fig 53. Remains of glandular epithelium surrounded by a necrotic area infiltrated with lymphocytes and polymorphs.

Histological preparations show destruction of the normal tracheal epithelium. The latter is normally a ciliated columnar epithelium based on a rather thick submucosa into which mucous glands dip towards a layer of smooth muscle. Figs 51 and 52 are taken from the trachea of a case of ordinary broncho-pneumonia. Apart from a round-celled infiltration of the sub-epithelial layer, there is no surface lesion, and the ciliated cells are intact. Figs 53 and 54 show the necrotic process of a staphylococcal influenzal infection which,

having destroyed the epithelium, has converted the entire mucosa into a mass of fibrin enmeshing necrotic cells and leucocytes and resembling granulation tissue. The remnants of the glandular epithelium persist. Sometimes the destruction is even more intense, and an apparently structureless membrane replaces all tissue down to the muscularis mucosæ (Fig. 55). Cocci are present in the necrotic material, and may show surface colonies.



Fig 55



Fig 56

Fig 55 —Trachea from another fatal case of fulminant staphylococcal-influenzal pneumonia (L P)
The necrotising process has converted the epithelium and submucosa into a structureless fibrinous membrane

Fig 56 —Bronchiole from same case as Fig 55 (L P)
The wall of the bronchiole is largely necrotic and the epithelium is replaced by granulation tissue Dark area represent colonies of staphylococci

The bronchioles exhibit a similar necrotising process, and may in fact be almost completely destroyed, as in Figs 56 and 62. Her the dark masses of cocci growing on the necrotic debris within th bronchiolar wall furnish a striking picture It is difficult to belie that such necrosis is the result of a process originating from with the lumen of the bronchiole, but the appearance in less-damage bronchioles suggest that destruction is greatest on the original

surface rather than throughout the wall, as would be the case if the lung had been destroyed by a thrombosing process

The lung itself shows microscopically œdema fluid (Figs 57 and 58) and intense congestion with alveoli choked with red cells or else an organising exudate of polymorphonuclear cells. Staphylococci occur in dark clusters of micro-colonies. Actual focal abscesses may be found, and these may appear to be based upon

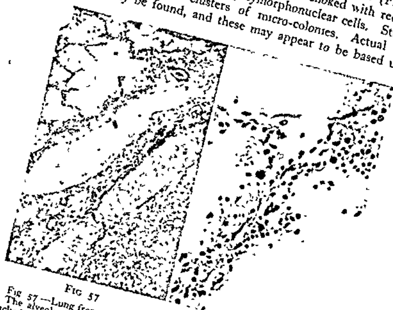


FIG 57 FIG 58

Fig 57—Lung from same case as Figs 55 and 56 (L P) The alveoli show widespread œdema Adjacent areas showed alveoli packed with red cells Colonies of cocci were scattered through the lung

Fig 58—High-power of Fig 57 Apart from alveolar œdema there is a negligible amount of cellular infiltration

spaces formed originally by terminal bronchioles, as in Figs 59, 60 and 61

This picture, which was described fully by Winternitz and others (1920) in the lung lesions of the 1918 pandemic, is indeed striking, and is quite unlike the histology of ordinary lobar or broncho-pneumonia The characteristic feature of the influenzal lung is the necrotising process of the surface ciliated columnar epithelium of the trachea and bronchioles, and it is, of course, this process which presents analogies with the lesions of influenza virus in the ferret or mice Attempts have been made by some authors to interpret the

histological lesions in the lungs of cases of influenzal pneumonia and to allocate responsibility respectively to the virus and bacteria concerned. Parker and others (1946) in Boston fully described the necrotising tracheitis and bronchiolitis in patients from whom *Staphylococcus aureus* and influenza virus were both recovered. They drew attention to the resemblance between their findings and



FIG. 59 FIG. 60

FIG 59 —Lung from a third case of staphylococcal-influenzal-pneumonia (L P)
Two small abscesses are seen in an area of intensely congested and œdematous lung

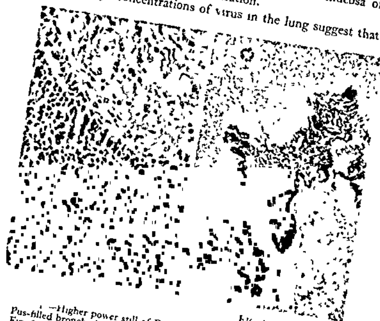
FIG 60 —High-power of FIG 59
The 'abscesses' are really pus-filled bronchioles. That on the left still has an intact epithelium, but on the right the bronchiolar wall has sloughed and colonies of cocci indicate its former position

those of Winternitz and others (1920) in the 1918 pandemic. Mulder and Verdonk (1949) and Stuart-Harris, Franks and Tyrrell (1950) described similar cases, and the Dutch workers found evidence of epithelial regeneration in the trachea which bore a close resemblance to the epithelial lesions of influenza in the ferret.

But no one has convincingly demonstrated that influenza virus unaccompanied by bacterial superinfection will produce a necrotic epithelial reaction in the trachea or bronchioles in man. Indeed, virus has been recovered from lungs both by Hers and Mulder (1951)

and by the author in cases where epithelial lesions of a necrotising character could not be demonstrated. This has made it extremely difficult to interpret such lesions in other cases There is no doubt that the influenza virus is present in the necrotic mucosa of the trachea, sometimes in high concentration.

Similar high concentrations of virus in the lung suggest that the



—Higher power still of Fig 60 Pus-filled bronchiole still retains its epithelium

Fig 62 —High-power of a bronchiole from Fig 56 Dark masses of cocci have infiltrated the necrotic wall of this bronchiole

FIG 62

virus is undergoing active multiplication, though the exact site of this is unknown. The necrotic lesions in the bronchioles of the ferret with influenzal pneumonia present a striking appearance. Hubble and Osborn (1941) picture a closely similar appearance in the lungs of two fatal cases of bronchiolitis during an influenza outbreak in Derby in 1940. There was the same destruction of epithelium nd plugging of the bronchioles with exudate, and though virus tests ere not made, bacteria were not recovered at post-mortem In iew of the analogy to bronchiolitis in the ferret and the probability that human bronchiolitis is rarely fatal, it seems likely that the usual site of attack by the virus in the lower respiratory tract is in the bronchioles rather than in the alveoli

Epithelial necrosis is not necessarily an invariable accompaniment of virus multiplication. Also, it has been shown that a virus such as the Newcastle disease virus of fowls, which does not multiply in the lungs of mice, may nevertheless produce lung lesions resembling influenza (Ginsberg, 1951). Strains of human influenza virus which do not undergo active multiplication in the mouse can also produce lung lesions in mice by some action possibly of a toxic nature, and this makes it impossible to argue that cell necrosis is always the result of viral multiplication. It is perhaps sufficient to point out the analogy between the comparative histology in the ferret, mouse and man and to await further work which may clarify the interpretation of observed phenomena.

Bacteriology of influenza and influenzal pneumonia

For some time after the first recovery of influenza virus in the laboratory the exact rôle of the virus was in doubt. The influence of those who believed in the importance of the *Hæmophilus influenzæ* was strong, and many believed that the virus was merely a symbiont of this bacillus Slowly the viewpoint began to change, and the facts that the hæmophilus was not regularly recovered in the garglings of cases of influenza virus infection and that human volunteers inoculated with virus alone developed clinical attacks of influenza made it impossible to believe in the significance of this, or indeed of other nasopharyngeal bacteria in uncomplicated cases of influenza.

A different story emerged in the cases of complicated influenza. The British investigation in 1937 (Stuart-Harris and others, 1938) suggested that influenzal bronchiolitis or bronchitis was sometimes a combined infection with *Hæmophilus influenzæ*, and this has neither been denied nor substantiated by other workers. The fact that such cases fail to respond sharply to antibiotic therapy probably indicates that pneumococci or hæmolytic streptococci are not concerned. A possible importance of *Staphylococcus pyogenes* exists, but has not been confirmed.

The bacteriological findings in patients with pulmonary consolidation are complex, but are of interest when compared with the findings in non-influenzal pneumonia Table 4 illustrates the bacteria identified in the sputum in 81 cases of pneumonia in Sheffield occurring in the winter of 1947–48, when influenza virus infection was not encountered. These patients were tested serologically, and failed to exhibit evidence of any recent influenza virus infection. As might be expected, the majority (81 per cent) yielded pneumococci in the sputum, and other organisms were unimportant ætiological

agents. A smaller series of 49 cases of pneumonia during a non-influenzal period in Sheffield between July and December 1950 gave closely similar results

TABLE 4

Bacteria Recovered in Cases of Pneumonia in Sheffield (Influenzal and Non-influenzal Periods)

Period	Number of cases	Pneumococci	Staph pyogenes	Hæm strep	Friedländer	No pathogenic bacteria
1 Non-influenzal						
(a) October 1947 to December 1948	81	66 (81)	2	2	0	15
(b) July to December 1950	49	38 (77)	5	2	0	10
2 Influenzal						
(a) January to March 1949	83	51 (61)	10	2	0	12
(b) January to March 1951	83	63 (76)	13	1	3	8
(c) Both influenzal periods Serologically and culturally positive cases of influenza virus infection only	55	39 (70)	20 *	2	0	3

* 7 had pneumococci as well
(Figures in brackets are percentages)

Two series of patients with pneumonia occurring in Sheffield during the influenzal periods of January to March 1949 and 1951 were similarly investigated Table 4 shows that among these patients pneumococci were also the predominant organisms (61 and 76 per cent), but that the staphylococcus was much commoner than in the non-influenzal cases Some of the cases with staphylococci in the sputa also had pneumococci, but the majority were unaccompanied by other pathogenic bacteria As has already been pointed out in Chapter 3, these cases of pneumonia during an influenzal season sometimes showed no relation to influenza virus infection, or else the infection accompanied or preceded the pneumonia In fact, 55 of the 166 cases in 1949 and 1951 were either synchronous with influenza A or else the latter preceded the pneumonia Thirty-nine (70 per cent) yielded pneumococci and 20 yielded staphylococci either alone or with pneumococci

The percentage of patients yielding evidence of pneumococcal infection is clearly much the same both in non-influenzal and influenzal seasons But an analysis of the actual serological types of pneumococci concerned in the two groups of cases yields an even closer resemblance (Table 5) The first eight types of pneumococci (I–VIII) are usually regarded as being the more highly pathogenic strains, and are encountered chiefly in cases of lobar pneumonia Among 107 typed strains of pneumococci in the non-influenzal series, 83 (77 per cent) belonged to Types I–VIII Among 117

TABLE 5

Types of Pneumococci in Cases of Pneumonia in Sheffield (Influenzal and Non-influenzal Periods)

	Total strains.	Types			Types I to VIII.	Re-mainder
		I	II.	III.		
Non-influenzal periods 1948 and 1950	107	24	21	13	83 (77)	24
Influenzal periods 1949 and 1951	117	21	15	20	85 (72)	32
Virus-positive cases only	39	7	3	5	24 (61)	15

(Figures in brackets are percentages.)

typed strains of pneumococci from the influenzal periods 85 (72 per cent) belonged to the same eight types of pneumococci. The resemblance between the two series is remarkably close. The cases of pneumonia yielding evidence of synchronous or post-influenzal virus infection in the two years numbered 55, and from these 39 strains of typed pneumococci were available for comparison. Of these, 24 (61 per cent) were of Types I–VIII. In these cases, therefore, a slight change in distribution of pneumococci may have occurred, but this was compensated for by the strains in the other cases during the same periods, so that the overall distribution was the same.

The conclusion arising from these studies is that the pneumococcus is the most important bacterial accompaniment of influenza virus in cases with pulmonary involvement. These pneumococci are approximately the same types of organisms as those encountered in cases of pneumonia all the year round. There is therefore no suggestion that a particular strain of pneumococcus is travelling along with the influenza virus as it passes from the nose or throat of one sufferer to another. One could explain the relationship better by assuming that just as pneumococcal infection often follows closely on the heels of the common cold, so also influenza virus infection produces those conditions in the respiratory tract which favour the pathogenicity of the pneumococcus.

A somewhat different conclusion emerges in the case of the *Staphylococcus pyogenes*. This organism is an infrequent pathogen in cases of pneumonia in non-influenzal seasons. It increases in importance during influenza virus epidemics. Moreover, there is some evidence that particular strains of the staphylococcus are then concerned. Bacteriophage typing as a method for the identification

of strains of staphylococci is a more recent technical acquisition than s pneumococcus typing by the aid of immune sera Bacteriophage yping of the strains of staphylococci recovered from cases of pner ionia in Sheffield and other areas during the three years 1949–51 w: irried out by Dr R. E. O. Williams (Table 6). A total of 5

TABLE 6

Staphylococcal Pneumonia 1949–51
(Sheffield and Other Areas)
54 cases

Influenza virus test	Number	Age		Recovered	Died	Staph phage type	
		<40	>40			52A	Others
Positive	24	5	18	15	9	12	8
Negative	21	8	13	10	11	5	16
Not tested	9	5	3	3	5	3	6
Total	54	18	34	28	25	20	30

patients were studied, of whom 45 were tested culturally or serologically for influenza virus No fewer than 24 yielded evidence of influenza occurring synchronously or shortly before the lung involvement Twenty-two were cases of influenza A, 2 were influenza B. It was found that the phage type 52A and closely related types occurred in two-fifths of all cases in which the staphylococcus was typeable and in three-fifths of the total strains from the virus-positive cases

This result would be meaningless without the background of the distribution of the staphylococcus types in healthy carriers and in the various clinical varieties of pneumonia Williams' figures (personal communication) for nasal carriers is that 20 per cent of the strains normally carried belong to the 52A type, whereas 19 (56 per cent) of his series of 34 cases of fulminant pneumonias yielded 52A It is therefore likely that the most serious form of staphylococcal pneumonia is related to this type of staphylococcus, which is less commonly found in the nose of ordinary carriers than in the sputum of the cases of pneumonia

This could arise either because of an enhancing effect of the influenza virus upon this variety of staphylococcus, or it could result if the 52A type is more virulent than other strains when introduced into the lung There is no evidence in regard to the latter point A series of experiments with staphylococci of both 52A and other types and influenza virus A in mice was carried out in my laboratory by

Dr. D. A. J. Tyrrell in 1950. He could not demonstrate any apparent additive effect between the staphylococcus and influenza virus in this species of animals. However neither the staphylococcus nor infl[illegible]
human diseas[illegible]

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CHAPTER 5

LABORATORY DIAGNOSIS OF INFLUENZA

THE methods of laboratory diagnosis of influenza can best be understood in the light of knowledge of the chief characters of the influenza viruses.

The chief characters of the influenza viruses A and B

The pathological effects of these viruses have already been described in Chapter 4, and the serological responses induced by them in their human or animal hosts have been mentioned. The viruses are demonstrable by electron-micrography, and purified preparations photographed by this technique show the presence of rounded particles and long filaments (Fig 63). The filaments are characteristic of preparations made from recently isolated viruses, whereas laboratory strains show chiefly round forms. The viruses belong to the middle range of size, being from 80 to 100 millimicrons in diameter. Their chemical composition is complex, but they consist largely of nucleoprotein. Carbohydrate is present, and so also is lipoid. Chemical differences are claimed to exist between influenza virus A and B (Knight, 1947). Both viruses are readily inactivated by chemical and physical agents such as phenol, formaldehyde and ultra-violet light. Both exhibit the remarkable phenomenon of hæmagglutination, which has provided a useful tool for serological and virus research. Analysis of the phenomenon suggests that it is caused by attachment of the virus particle to certain areas on the surface of the red cell and that a similar attachment may occur to tissue cells, particularly to cells of the respiratory tract. It is believed that the columnar ciliated cell is thus singled out for adsorption by the influenza virus particle and hypothetical receptors consisting of mucopolysaccharides are believed to exist on the cell surface. The receptors on the red cell or on surface cells appear to be destroyed by the virus by means of an enzyme system, and living virus will destroy the red cell receptors, and thus render it subsequently inagglutinable by other agents. Adsorption to a cell probably precedes penetration of the cell wall by the virus, but enzymatic destruction of the surface receptor is not an essential step prior to penetration into the cell. The virus antigens are complex, and both influenza virus A and B consist of a group of related

with demonstrable specific antigenic differences between individual strains Thus, the original virus A (W.S strain) recovered in 1932 was apparently serologically distinct from the strains found from 1934 to 1943 (PR8-like strains). But since 1946 nearly all the virus A

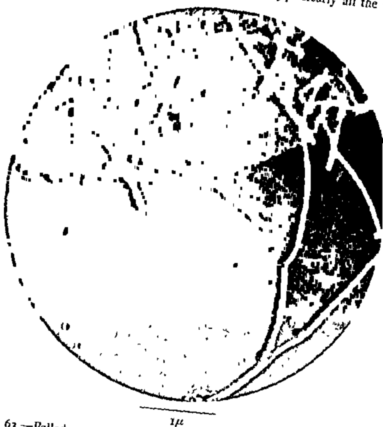


FIG 63 —Palladium shadow-cast electron micrograph of influenza virus A (1949 strain recently isolated in eggs), adsorbed on laked fowl red cell membrane × 34,000 approx.

strains recovered all over the world have belonged to a serological group easily recognisable from the earlier viruses, and hence termed the A prime viruses Similar but less sharply defined differences exist between the influenza virus B strains. No group antigens connecting the A and B groups have been found, but the 'soluble' antigen of the A viruses is common to the A group, and similarly for the 'soluble' antigen of the B group

Controversy exists concerning the nature of the soluble antigen

which some regard as a degradation product of the virus and others as a precursor form preceding the development of the virus particle. It is much smaller in size than the virus particle, being not greater than 35 millimicrons in diameter approximately. It does not produce hæmagglutination. The substance responsible for hæmagglutination appears to be the virus particle itself.

No comparable epidemiological or clinical differences exist between the various influenza outbreaks from which strains of virus differing antigenically have been recovered. Nor have the viruses exhibited any striking biological differences, though in the laboratory the strains are remarkably plastic. Highly virulent or attenuated strains have been developed in the laboratory, and a variant strain of the W.S. virus which will proliferate in the mouse-brain and cause death from encephalitis has also been cultivated (Stuart-Harris, 1939). Another property of virus strains which appears to vary is that of toxicity. Highly purified concentrated preparations of virus will kill mice if given intracerebrally, intravenously or intraperitoneally, the mice having developed lesions of the brain, liver or spleen (Henle and Henle, 1946). Similarly, febrile responses can be demonstrated in rabbits, and occur also in man, even when inactivated virus of high concentration is used. This toxic property is not possessed in equal measure by all strains of virus.

The influenza virus C

Taylor (1949) described the recovery of a strain of virus labelled 1233 in March 1947, from a patient with a mild attack of influenza. He found it to be antigenically distinct from influenza virus A and B. It grew poorly in the chick embryo, requiring amniotic passage. Cultivation in the allantoic cavity gave irregular results. Taylor also found positive antibody responses to the agent in two sera from cases of respiratory illness in Venezuela. In March 1950, Francis, Quilligan and Minuse (1950) isolated another strain of a virus closely related to the 1233 strain from an outbreak of influenza. Serological responses to the virus were demonstrated with sera from children ill with influenza during an outbreak in 1946–47. The majority of cases of influenza in this outbreak were due to influenza A prime virus, however. Relatively high antihæmagglutinin titres against the new virus were found in samples of serum from adults collected as far back as 1936, and Francis concludes that the virus has been in existence therefore for some years.

The virus itself has been studied so far only in the chick embryo. Cultures in the amnion give high infective titres, but the hæmag-

TABLE 8

Complement-fixation Test (Soluble Antigens) with Sera from 1951 Cases of Influenza

Patient	Serum	Dilutions serum v. Infl. virus A: 4	8	16	32	64	128	256.	Control.	Titre	Titre v. Infl. B.
M 69	A	+++	[illegible]	o	o	o	o	o	o	6 } × 4	<4
	C	++++	++++	+++	+	o	o	o	o	24 }	<4
M 70	A	o	o	o	o	o	o	o	o	<4 } × 48	<4
	C	++++	++++	++++	++++	+++	+	o	o	96 }	<4
M 89	A	o	o	o	o	o	o	o	o	<4 } × 64	<4
	C	++++	++++	++++	+++	o	o	o	o	32 }	4
M 98	A	o	o	o	o	o	o	o	o	<4 } × 12	<4
	C	++++	++++	+++	+	o	o	o	o	24 }	<4
M 116	A	o	o	o	o	o	o	o	o	<4 } × 16	4
	C	++++	++++	+++	++	o	o	o	o	32 }	4
Human Convalescent Infl. A		++++	++++	++++	++++	+++	++	o	o	128	<4

A = acute C = convalescent
+, ++, +++, ++++ = degrees of fixation of complement.
o = complete lysis
Infl. virus A used was the W.S. strain. Infl. virus B was the Lee strain.
Note confirmation of diagnosis including M 70

example of the end-result of a test when a number of pairs of sera from 1951 cases of influenza were titrated against an influenza virus A prime strain.

The complement-fixation test consists in the examination of sera for complement-fixing properties in the presence of an antigen containing virus. The latter is most easily prepared from infected hens' eggs, but mouse-lung antigens can be used if eggs are not available. Two types of influenza virus antigen with complement-fixing properties exist—namely, the virus particle itself and a much smaller particle devoid of infecting and hæmagglutinating properties ('soluble' antigen of Fairbrother and Hoyle, 1937). From the standpoint of diagnosis it is best to use the latter antigen, as the former is rather too specific serologically. The 'soluble' A antigen is common to all the various strains within the serological groups of A viruses, and similarly for the B antigen. Hoyle (1948) describes the preparation of the antigen from mouse lungs, but a high-titred antigen can be prepared from the allantoic membranes of twelve- or thirteen-day chick embryos inoculated twenty-four hours previously with a heavy concentration of seed virus. The membranes are washed, minced and ground in a small volume of saline. After being frozen and thawed three times, the emulsion is centrifuged, chloroform is added to the supernatant and it is allowed to stand in a refrigerator overnight. The supernatant from a further centrifugation is distributed in ampoules, frozen and dried. Sodium azide in a final concentration of 0·08 per cent is used as a preservative. The antigen is labile when in the liquid state even when stored at 2° C. It is reconstituted and titrated as described for the mouse-lung antigen by Hoyle (1948). Pairs of serum samples are then diluted and tested in the presence of the optimum antigen concentration. The result of a test with sera from 1951 is shown in Table 8. The end-point is taken at a roughly 50 per cent hæmolysis.

Interpretation of serological results

Diagnosis is based upon the demonstration of a four-fold or greater concentration of antibody in the convalescent serum compared with that present in the first serum. Two-fold increments in titre only just exceed the technical variation, errors in dilution and so on and are regarded as a negative result. It would be of great advantage if reliance could be placed upon the absolute titre of antibody demonstrated by either *in vivo* or *in vitro* methods. But the presence of antibodies which neutralize the virus and inhibit agglutination in most adult sera makes this impossible. The inhibition test also detects

one or more constituents of normal serum which are not the same in composition as antiviral antibody. In the case of the complement-fixing antibody to 'soluble' antigen, the titre wanes rapidly after infection, so that a titre of 1 in 16 or more in a single specimen can be taken as an index of recent infection It is, however, still more reliable to demonstrate a rise in antibody, and this criterion was used in determining the presence or absence of infection in the investigation of various outbreaks recorded in Tables 9–11.

Mouse neutralization tests were used in the investigation of epidemics of influenza in 1937, 1939 and 1941 (Table 9). Strains

TABLE 9

Mouse Neutralization Tests

Year	Virus recovered	Positive	Negative	Total cases
1937	A	20 (85) (Infl A)	3 (15)	23
1939	A	20 (31) (Infl A)	40 (69)	63 *
1941	A	27 (79) (Infl A)	7 (21)	34

* Re-examination of 38 sera in 1941 gave 17 positive results (9 Infl A, 8 Infl. B)
(Figures in brackets are percentages)

of influenza virus A were recovered from garglings in all three years A high proportion of positive serological results was found in 1937 and 1941. The epidemic of 1939, however, gave a much lower incidence of antibody rises against influenza virus A. Re-titration of some of these sera against influenza virus B was carried out in 1941 (Lush and co-authors, 1941) and several instances of antibody increase to this virus were demonstrated But 55 per cent of sera were still negative, and these illnesses remained of undetermined ætiology

Hæmagglutination-inhibition tests were employed from 1942 onwards, and the results are recorded in Table 10 of the investigation of two epidemics of influenza B and three of influenza A. The B epidemics gave positive serological results in about 50 per cent of instances using one virus strain only (Lee virus isolated in 1940 by Francis) The A epidemics gave about 60 per cent positive results by the hæmagglutination test, but two virus strains were employed—the standard laboratory PR8 strain isolated in 1934 (Francis, 1934), and a strain of the influenza A prime group Instances existed of a

titre in the serum. Thirdly, the serological response to infection is occasionally highly specific, and perhaps can only be detected if the virus strain responsible for infection is used in the serum tests. The greater the number of antigens and of tests, the greater therefore will be the number of cases of influenza detected serologically. Use of the 'soluble' antigen in the complement-fixation test reduces this difficulty to a minimum. However, a residue of serologically negative cases still exists even when this latter technique is used, and the explanations given above may account for these. It will in any case be obvious that co-existence of acute respiratory diseases of the febrile catarrh variety and of influenza in any community is perfectly feasible.

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CHAPTER 6

EPIDEMIOLOGY OF INFLUENZA

HISTORICALLY, influenza has been recognised by its power of rapid dispersion throughout the population of whole countries and by the explosive character of its epidemics. Yet, small localised outbreaks with little tendency to spread outside the affected community have long been known to occur, nor has the individual epidemic invariably been explosive. Perhaps, however, the most baffling feature of influenza is the tendency for occasional conflagrations to develop into epidemics affecting most of the globe. Such pandemics as have occurred in recent years have been clinically similar to localised outbreaks in general characteristics, but the earlier pandemics of 1890 and of 1918 exhibited exceptional morbidity and mortality. The tremendous destruction in these latter pandemics, particularly in young adults in the case of the 1918 pandemic, indicates a power to kill on a world-wide scale unequalled by any other contemporary disease. In fact, students of the almost trivial type of influenza encountered in the past twenty years may well be pardoned if at times they wonder whether the virus of pandemic 1918 influenza can really have possessed any relationship with known influenza virus strains of today. Before discussing such matters in detail, however, it will be well to examine the background of epidemiological experience in Great Britain and elsewhere in the period before and since the discovery of the influenza viruses.

Fig. 65 illustrates the experience in regard to deaths from influenza in England and Wales over a period of 90 years from 1850 onwards. Though large-scale epidemics had been experienced before 1850, there was an apparent lull amounting almost to extinction of the disease in the period just before 1890. Then, in 1890, the pandemic caused a sharp rise in the level of prevalence, and incidence has remained ever since at a higher level than before 1890. Superimposed on the base-line of inter-epidemic incidence periodic outbreaks have occurred every two or three years, and this periodicity has continued up to the present. Recent history since the first isolation of influenza virus has been one of major epidemics at periods of four to eight years, with lesser epidemics in intermediate years, and the base-line in between epidemics has tended to fall. Incidence in 1948 was thus the lowest since 1918, while major epidemics

occurred in 1933, 1937, 1943 and 1951. Medium-sized outbreaks of lesser size have occurred at intervals in between these years

Until it was possible to recover strains of influenza virus and to determine their exact antigenic composition, little understanding of the periodicity of the disease was achieved, particularly since it became apparent at an early date that the two main antigenic varieties —influenza A and B—occurred apparently independently The recovery of these viruses over the last eighteen years in England and

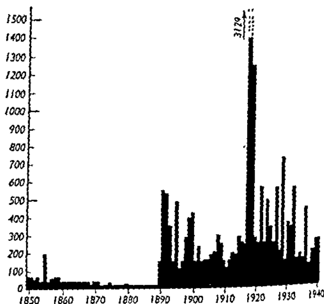


FIG 65 —Influenza deaths per million from 1850 to 1940 (England and Wales)

(The column for 1918 is double the height indicated)

Wales is indicated in Fig. 66 in relation to individual epidemics It is clear from this chart that all the major epidemic waves have been associated with influenza virus A, while minor prevalences have been due either to A or to B Only one moderately large epidemic associated with influenza virus B has been experienced in Great Britain since the year 1940, when the virus was first isolated in the U.S A. This was the epidemic of 1945-1946, which had a peak in mortality of 304 in one week among the 126 Great Towns with a population in excess of 50,000, and ranked as a medium-sized epidemic. In these years since 1932 there was only one influenza epidemic in which no strain of influenza virus was recovered in Great Britain This was the epidemic of 1940, when, owing to

difficulties associated with wartime mobilisation, the outbreak was not studied in detail. With this exception, it is seen that in every year when the deaths from influenza in the Great Towns have exceeded 100 in any one week, one or other of the influenza viruses was recovered in the laboratory. In the intervening years of endemicity no virus either of influenza A or B was usually recovered even from sporadic cases of clinical influenza or from local outbreaks of respiratory disease.

The pattern of prevalence which has emerged from these national statistics has been that of somewhat irregular periodicity both of influenza A and B, with almost complete disappearance of the viruses in between outbreaks. Though some order has become obvious, in that influenza A epidemics have recurred every two or three years and influenza B at two-, four- or six-yearly intervals a major epidemiological problem has emerged. This is no less than the problem of determining the origin of epidemics which is, of course, linked with the locus of the virus in between epidemics. Among other epidemic infections involving the respiratory tract, conditions such as diphtheria and measles may be contrasted with influenza. The laboratory detection of the diphtheria bacillus is, of course, extremely exact, and has enabled the bacillus to be detected in healthy human carriers quite apart from actual cases of the disease. Diphtheria thus is known never to disappear from the population in between epidemic prevalence. Similarly, clinical detection of measles depends upon recognition of a characteristic physical sign—the rash —and experience indicates that the periodic recurrences of measles are based upon an endemicity with constant persistence of the virus in the population as shown by clinical cases of infection. Now, although influenza similarly appears to be present clinically every year, recovery of virus in the laboratory, or evidence of infection furnished by the more delicate serological studies of the population, suggest that the virus becomes quiescent once an outbreak of infection has subsided Sufficient evidence of sporadic case occurrence exists, however, for it to be said that the virus is not entirely extinct. But, from an incidence only detected by large-scale surveys, the virus infection develops into an explosive outbreak, without any apparent intervening steps of increasing prevalence.

The origin and spread of epidemics

So long as the study of influenza was confined to individual countries this problem of the emergence of outbreaks remained unsolved, but two contrasting theories have been evolved. The first,

or latent virus theory, is that the virus 'goes underground' at the end of a period of epidemic prevalence. It exists, that is to say, in some form of latent infection, perhaps in some remote corner of the respiratory tract or in an animal reservoir, in which state it cannot be detected by normal methods of investigation. This theory has received a good deal of theoretical support from the studies carried out by Shope on the analogous disease of swine influenza (Shope, 1941, 1944)

This disease appeared in the Middle West of the U S A. shortly after the 1918 human pandemic of influenza. It exists in the form of explosive annual winter epidemics in States such as Iowa at the present time. As stated already, it is due to a simultaneous hæmophilus and virus infection Direct search of pig-tissues in between epidemics reveals no trace of the virus Yet, earthworms collected on the pig-farms in Iowa appear to harbour swine influenza virus in a masked form Pigs bred and kept in isolated laboratories in New Jersey, and fed on earth-worms dug up in Iowa, develop a latent state of infection with the virus. If they are then 'shocked' by some procedure such as inoculation with a bacterial vaccine, swine influenza develops, and the virus can now be demonstrated in its normal infective form in the pig's respiratory tract Shope considers that natural epidemics thus arise from latent virus pre-seeded before the epidemic, and he has shown that the common lungworm of the pig is the agent concerned in passive transmission of masked virus from the convalescent pig to the earthworm, and thence back into the pig, and in particular into the lung No similar mechanism has yet been demonstrated in the case of human influenza, and no helminth parasite is known, whose life-cycle could furnish a similar transmitting agent to the respiratory tract Yet the explosive human epidemic certainly is in favour of some form of pre-epidemic seeding of virus which has so far been undetected Nor must it be forgotten that swine influenza virus is a close serological relation of human influenza virus A

The second theory concerning the persistence and spread of human influenza is that the virus exists by a continual case-to-case transmission This presupposes that there is always an outbreak of influenza somewhere in the world, and that as influenza dies out in one country, it develops anew in another area The alternation between the winter seasons in the Northern and Southern hemispheres furnishes a possible mechanism for the continuous survival of virus, as also do studies of the spread of epidemics from country to country Before 1947 the geographical correlation of

epidemics was based on purely epidemiological considerations Strains of influenza virus were being recovered regularly from the U.S.A., certain parts of South America, Australia, South Africa, and parts of Europe. When the time-relationships of these epidemics were correlated with the types of virus recovered, the probability of geographical spread of particular strains emerged Thus the influenza B outbreak of 1945–46 affected wide areas of the Pacific and the U.S.A. in the form of successive local outbreaks, with time intervals favouring a continual chain of transmission. Yet the major outbreak of influenza A in the U.S A., Canada and Great Britain in November 1943 appeared to involve geographically remote areas almost simultaneously, and too rapidly for any chain of infection to have occurred. These facts led to the development by the World Health Organisation in 1947 of a chain of reference laboratories throughout the world linked with two major study-centres in London and in New York. The story of the two epidemics studied so far is a fascinating one, and will repay detailed description.

A European epidemic developed in 1949 which produced a high incidence of infection in many of the large cities of Italy and France. Influenza was also experienced in Austria, in Holland, Great Britain, Iceland and Sweden. The time of occurrence of epidemics strongly suggested spread from an initial focus of infection in Sardinia to the mainland of Italy, and thence northward to France and Great Britain and eastwards to Austria (Chu and others, 1950) (Fig 67) The epidemic developed first in southern coastal towns in England and travelled northwards during the next three weeks. All the strains of virus recovered from the various European centres and parts of England were closely related antigenically, and belonged to the sub-group of influenza known as the A prime type The puzzle was that the epidemic in Sardinia appeared in the north of the island and involved shepherds in remote mountain areas simultaneously with the larger towns No clue existed as to the reason for the development of this outbreak in Sardinia.

The 1950–51 epidemic (Freyche and Klimt, 1951) differed in several important features from that of 1949 In the first place, it involved a much wider area of the globe, and affected Europe, Africa, the United States, Japan and Oceania (Fig. 68). In Europe, the epidemic began in Sweden and Denmark in October 1950 Influenza had in fact occurred in parts of Sweden in the form of local outbreaks in June and July 1950, the virus recovered then was an influenza A prime type, and a closely similar virus was recovered from the renewed outburst of infection in November. The winter

epidemic was a mild one in Scandinavia, though it involved all three countries. Ports in Great Britain which are concerned with trade from Scandinavia developed influenza shortly before Christmas, Newcastle and Aberdeen being affected almost simultaneously Again the epidemic was a mild one. At approximately the same time, however, Liverpool and Belfast also reported influenza, but in these places the outbreak took a much more serious course. The morbidity was exceptionally high, and a large number of pulmonary



FIG 67.—The spread of influenza virus during the European epidemic of 1948–49

(After Andrewes, C H, *Edin med J*, 1949, 56, 345)

complications occurred, particularly in the elderly The deaths from influenza and from all causes rose to figures greater than those experienced in Liverpool in the 1918 epidemic But, the age-incidence of the mortality was almost wholly in those over fifty-five years of age

In spite of the intense epidemics in the North of England, the infection spread irregularly and in mild form throughout the rest of the country, but the figures from the north caused the total mortality to be greater than that of any epidemic in the previous fourteen years A high mortality was also experienced in Spain, but elsewhere the epidemics in Europe, Africa, Asia and America were not unusual in character, and the pandemic must rank as a normal mild

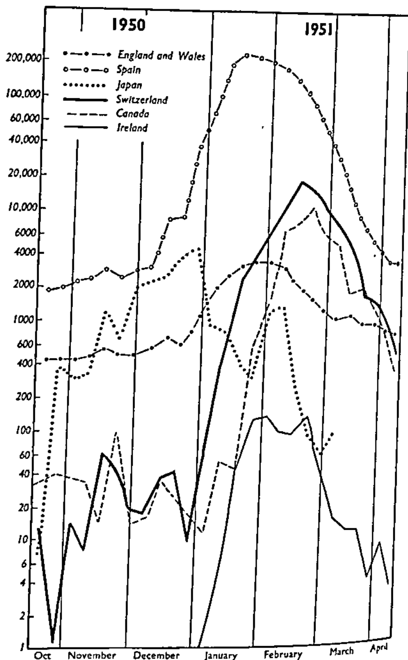


FIG 68 —The 1950–51 pandemic of influenza

Weekly cases of influenza in the countries indicated
(Modified after Freyche, M J, and Klimt, Ch 1951 *Epidemiological and Vital Statistics Report*, World Health Organisation, Vol. 4, p 140)

type of influenza. During the pandemic, strains of influenza virus were recovered and sent to the World Influenza Centre in London from many countries As in 1949, all the strains belonged to the influenza A prime group, but two distinctive sub-groups were differentiated (Isaacs and Andrewes, 1951) One of these included the Scandinavian strains, the other the strains recovered from Liverpool and Belfast The difference between these strains fitted in with the view that one group of epidemics arose from the source of latent infection in Scandinavia from the previous summer epidemic, but that a new importation from the Southern hemisphere or the East accounted for the virulent Liverpool epidemic If these facts are upheld by subsequent experience, it suggests that influenza has two modes of survival In the first mode it survives in latent form in the community, so that it goes underground during the summer heat. But the second mode is one of a continuous chain of infection with crossing of the equator in reverse order to that of the sun, so that the virus persists in the winter seasons of either the Northern or the Southern hemisphere No one can say which of these two modes of survival is the favourite method adopted by the virus, but it is clear that global study of influenza epidemiology is the only way to solve the problem of the origin of the epidemic

One fact established already is that spread of infection from one area or country to another often appears to occur by direct geographical contiguity rather than along lines of communication such as afford a more rapid chance of infection Yet in rural areas the importation of infection can often be attributed to a particular individual or group of persons who return to their homes after staying in a town where influenza is already established Pickles (1939) quotes the case of the school in Wensleydale which in 1937 suffered an explosive outbreak of influenza forty-eight hours after the village schoolmistress returned from a town No other cases of influenza were present in the village at the time, the schoolmistress herself suffered only a mild attack, but it was highly probable that she was responsible for introducing the virus into the school Similar instances have been brought together by Hare and Mackenzie (1946) Further consideration of the subject of the mode of transmission of influenza will be found in Chapter 13

General characteristics of influenza epidemics

(1) **Variation in attack-rate: the factor of immunity.** Much of the information described above has been gathered together on the basis of mortality statistics, for influenza as such is not a notifiable

disease in Great Britain The actual information available concerning the morbidity of an epidemic is therefore somewhat meagre. Every doctor knows the impact of the epidemic of influenza on his or her practice, but few have kept records from which a picture of the course and effect of the epidemic can be built up.

The series of isolated villages in Wensleydale among which

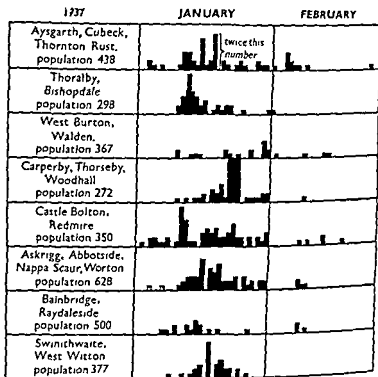


FIG 69 —The 1937 epidemic of influenza in Wensleydale, Yorkshire

(Reproduced by kind permission of Dr W N. Pickles, Aysgarth)

Each solid square records an actual case of influenza. The open squares were cases of diarrhœa and vomiting Ten squares placed vertically on top of each other fill the space between the horizontal lines

Dr. W. Pickles has practised for forty years constitutes a microcosm of the country as a whole Pickles's records cover the period from 1935 onwards, during which time the villages have experienced three major epidemics of influenza and several minor ones From his records it is clear that the epidemic of 1937 was the most intense outbreak during the entire period, and Fig. 69 is an exact reproduction of the records of this epidemic. Two features are important First, the incidence was high, and ranged from 3 6 per 100 to 21·3 per

100 in the various villages Secondly, the infection appeared to exhaust the capacity of the human herd to respond clinically to other ailments, and the epidemiological record carries no instance of any other infectious disease during a period of weeks Several other points emerge from the detailed analysis of Pickles's records concerning influenza epidemics (Table 12). There were low records of incidence in 1937

TABLE 12

Yearly Attack-rates from Influenza per 100 Population in Villages in Wensleydale

	1933	1937	1943
Aysgarth (438)	1 37	17 81	4 11
Thoralby (298)	6 38	13 76	6 71
West Burton (367)	14 17	5 72	3 81
Carperby (272)	1 84	21 32	7 72
Redmire (350)	1 14	20 28	12 29
Askrigg (628)	2 87	11 31	9 24
Bainbridge (560)	5 4	3 6	7 2
West Witton (377)	4 24	9 28	3 45

Modified after Pickles, W N, Burnet, F M, and McArthur, N *Journ Hygiene*, 1949, Vol 45, p 472
(The three years chosen were years when influenza A caused large epidemics in England and Wales)
Population figures in brackets

in two villages—Bainbridge (attack-rate 3 6 per cent) and West Burton (attack-rate 5 7 per cent). Both these villages suffered relatively more severely from influenza during the previous influenza A outbreak in 1933 Their percentage incidences were then 5 4 and 14 17 In this year Aysgarth had 1 37 per cent, Carperby 1·84 per cent and Redmire 1 14 per cent attack-rates, and during 1937 their respective rates were 17 81 per cent, 21 32 per cent and 20·28 per cent Table 12 shows the epidemic experience in all these villages during three years of epidemics before and after 1937 These attack-rates have enabled Pickles, Burnet and McArthur (1947) to formulate the following view concerning the duration of herd immunity following an epidemic of influenza Their data strongly suggest that group immunity in a small community may be sufficiently high four years after an epidemic of influenza to confer a significant resistance to infection in a renewed epidemic of the same serologic type of the disease This view affords an important explanation of the variable incidence of influenza during one and the same epidemic in similar but separated semi-isolated communities Fig 70 shows outbreaks of influenza A in different Army units of approximately the same strength Similar variations are encountered in school outbreaks during the same epidemic There is no apparent reason why a

particular school should suffer intensely and a neighbouring one should escape lightly, but the factor of herd immunity cannot readily be assessed, and it seems probable that this may be important in the determination of the attack-rate during a widespread epidemic

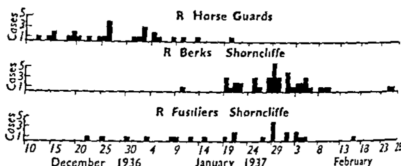


FIG. 70 —Influenza epidemics in three Army units

The three units each comprised approximately 300 men The attack-rates were 9 per cent (Horse Guards), 14 per cent (R Berks) and 8 per cent (R. Fusiliers) The form of the outbreak varied in each unit. Each column represents the daily number of new cases

During the more restricted epidemics of influenza A or B which occur in between the major outbreaks, particular communities experience an even more variable incidence of infection. The author has been particularly impressed with the intensity of infection in some epidemics of influenza B occurring in schools During the moderate outbreak in the general population of influenza B in 1946, many boarding-schools and preparatory schools experienced heavy attack-rates and explosive epidemics (Table 13). A strikingly

TABLE 13

Epidemics of Influenza B in Residential Schools, January–February 1946

School	Ages of scholars.	Number at risk.	Cases of influenza	Attack-rate, per cent
*Micklefield (girls)	7–12	74	29	39.2
*King's Mead (boys)	7–12	71	41	57.7
*St Peter's (boys)	8–13	76	34	44.7
*Ladycross (boys)	7–13	101	21	20.8
Canford (boys)	13–18	300	115	38.3
Christ's Hospital (girls)	9–17	288	40	13.9
Christ's Hospital (boys)	9–17	825	157	19.0
Haileybury (boys)	13–18	528	176	33.3

Analysis of attack-rate at different ages at Christ's Hospital (boys) indicated a variation from 16 to 24 per cent in the various age-groups All ages were affected at this and the other schools * Preparatory boarding-schools at Seaford

One school at Seaford with eighty-five girls aged 5–17 had no outbreak during the entire period

explosive outbreak was also witnessed in February 1950 at a girls' boarding-school during a minor outbreak of influenza B in the general population (Fig. 71). The attack-rate in this school, where the children ranged in age from five to eighteen years, was 60 per cent in three weeks. Similar intense localised outbreaks of influenza A have also been encountered Thus Fig 71 also shows incidence in two Army camps in England during influenza A epidemics in 1947; the attack-rates were 20 per cent. Though this was the first year when the influenza A prime viruses were recovered in England, the general

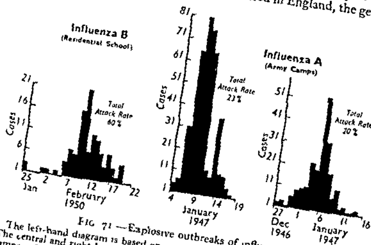


FIG 71 —Explosive outbreaks of influenza

The left-hand diagram is based on an outbreak of influenza B at a girls' school The central and right-hand diagrams are of influenza A prime outbreaks in Army camps In each case the columns represent the daily number of new cases

population suffered only a minor outbreak Indeed, the experience of epidemics in these semi-isolated school and Service communi suggests at times an inverse relationship of incidence with that of infection in the general population Thus in 1949, when the gene epidemic of influenza A was considerable but not exceptional, t Army garrison at Catterick suffered an explosive wave produci several hundred cases During the more severe general epidemic England in 1951 this garrison had only a mild outbreak, in both yea the epidemic was one due to the influenza A prime viruses It is no impossible that herd immunity may have been important in this camp, but as so much of the population was composed of recruits with a relatively short period of stay, the situation is not comparable with that of the Wensleydale villages

Little or nothing is known concerning certain factors which may determine the intensity of outbreaks among particular communities It is usual to speak of overcrowding as an important factor, in view of its probable influence on the transmission of air-borne infection. There are, however, no convincing data on the influence of overcrowding on the incidence of epidemic influenza But there is evidence (Breese and others, 1945) that the number of individuals housed in a room is of greater importance either than floor or air-space in relation to upper respiratory disease in a barracks Secondly, the circumstances of age and sex often influence the incidence of other infections, but in the case of influenza, such data as are available point to little variation of a systematic character. A recent analysis was made by Hope Simpson (1951) of the age distribution of influenza in 1951 in 100 families compared with the age structure of the practice in which the observations were made After one case had occurred in the family, the age distribution of the subsequent cases was studied. Escape from infection was more frequent in those aged 20–40, but there was involvement to a greater or lesser degree at all ages. Similarly, sex incidence, at any rate in schools, is not significantly variable, apart from the variations in attack-rate likely to be experienced in any case

A set of circumstances which appears, however, to be important in relation to the incidence of influenza is that concerned with a change in the composition of the particular human herd. This is, of course, the factor discovered by Greenwood and others (1936) to be of major importance in connection with the experimental epidemics which they studied in mouse populations. During the influenza epidemic in 1937, comparative attack-rates in Naval establishments strongly favoured the view that recruits suffered a much heavier incidence of infection than did trained men. A contrary experience was recorded in military establishments in the U S.A. during the general influenza A epidemic in 1943. It is therefore not certain that the factor of residence or of seasoning is as significant in the case of influenza as it may be in other infections. But the epidemic of influenza A on Ocean Island described by Isaacs and others (1950) may be quoted as throwing some light on the influence of the composition of the population. Isaacs studied an epidemic which broke out among the Polynesian natives from the Gilbert and Ellice Islands resident on Ocean Island shortly after the arrival by ship of a batch of Chinese labourers. The latter were segregated in quarantine for twenty-four hours and were then released. Within nine days of their release an epidemic of considerable intensity broke out

among the native Gilbert and Ellice islanders who had arrived on the island twelve months before, and no case at all occurred among the Chinese. Yet there had been no apparent clinical cases of influenza among the Chinese labourers during their voyage, which had taken three weeks. It seems that both Polynesian and Chinese groups of people had achieved considerable stability in their herd composition prior to their intermingling. But the result of interchange between the two groups was the violent breaking out of infection in only one of the herds. Similar circumstances may well operate in the case of recruits to Army garrisons, and may account for an apparent disparity of incidence in trained men and recruits.

Finally, there can be little doubt of the importance of individual immunity in regard to infection and its incidence. Yet influenza virus infection induces only a temporary immunity in man, as in the ferret. Moreover, influenza A and B do not cross-immunize against each other, so that during mixed outbreaks of A and B individuals may suffer double attacks or simultaneous double infection (Burnet, *et al*, 1946; Kilbourne, *et al*, 1951). The degree of cross-immunity between different strains of influenza virus A after infection with that virus is unknown. However, the antibody response in natural infection with influenza A is a broad one, and it is unlikely that the immunity is developed strictly against the infecting virus strain. This does not hold, however, for artificial immunity produced by vaccines, as will be made clear in Chapter 13.

It seems reasonably clear that immunity to natural infection depends upon the possession of antibodies capable of neutralizing the virus, and perhaps also upon some as yet undefined natural defence mechanism of the respiratory tract. The experiments of Fazekas de St Groth and Donnelley (1950) on mice, indeed, suggest that the most important factor in immunity is the titre of antibody present in the surface secretion of the respiratory tract. Such antibody is known to exist in man, but is masked in hæmagglutinin tests by other substances, such as mucin, which are actively inhibitory to the virus *in vitro*. However, these latter inhibitory substances are rarely effective in preventing experimental infection of cells of laboratory animals by the virus, as is neutralizing antibody. But it is still far from clear whether neutralizing antibody in the secretions, which is presumably derived at least in part from the serum antibody, bears a quantitative relation to the latter. There are certainly instances where infection does not occur during epidemics in individuals with a low titre of antibodies in the serum, and the converse of infection in the presence of a high titre is also

encountered. On the whole, however, a general correlation exists, in that infection is commoner among the group of individuals in the community with low antibody levels than in those with high titres. Much more work is still required on this vital subject of the factors chiefly concerned in human immunity.

Meanwhile, the period of duration of immunity is also unknown. After artificial infection of volunteers, reinfection may be possible as early as four to nine months later. Such infection is, however, an overwhelming one, produced by deep inhalation of virus, and is hardly comparable to infection by normal contact. Natural immunity is certainly as long-lived as a year, and it may be much longer. However, schoolboys who experienced an attack of influenza A during an epidemic in 1947 again contracted an A infection by a serologically identical virus in 1949 (Sigel and others, 1950) Evidence has already been quoted that group or herd immunity in a community may be longer lasting, perhaps for as much as four years (Pickles, Burnet and McArthur, 1947). It seems reasonable to relate freedom from infection partly to the quantity of contagion encountered during exposure. Frequent exposure to multiple sources of infection, such as must occur during large epidemics, will be more likely to break down the defence mechanism than a solitary exposure to a single source.

(ii) **The mortality during influenza epidemics.** The impact of an epidemic of influenza virus infection on a community of the size of a town is shown by the increase in morbidity just as in the case of rural villages But, in towns, a feature which attracts particular attention is the increase in numbers of deaths. This increase, which affects deaths from all causes as well as deaths certified as being due to influenza or to its complications, is now understood to be a characteristic of influenza virus infection compared with that of the other epidemic respiratory tract conditions Indeed, the certified deaths from influenza in the Great Towns of England and Wales have furnished a sensitive indicator of the presence of influenza virus infection in the community. Recent experience (Martin, 1950) in the trend and character of mortality during epidemics (Fig 72) has shown a tendency for a fall in the height of the peaks and in the level of the troughs The low level reached in the period 1945–49 recalls the trough experienced between 1876 and 1890, which was followed by the outburst of the pandemic of the latter year. No explanation is forthcoming for these cyclical changes in mortality, and though experience in recent years may have been modified by the use of sulphonamides and

penicillin, it seems clear that this is not the whole explanation. Logan and MacKay (1951) have drawn attention to another feature in the

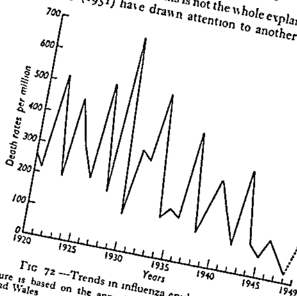


FIG 72 —Trends in influenza epidemics 1920–49
The figure is based on the annual death-rate from influenza per million in England and Wales
(After Martin, W J, 1950, *Brit med J*, 1, 267)

epidemic curve which seems to be changing This is the rate of increase in numbers of deaths (Fig 73), which shows a recent tendency to produce a steeper curve than that experienced twenty or more years ago This has resulted in a decrease in the time elapsing

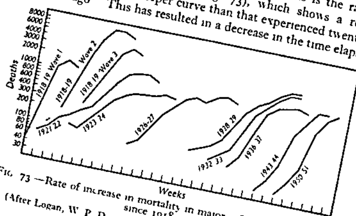


FIG 73 —Rate of increase in mortality in major influenza epidemics since 1918–19
(After Logan, W P D, and MacKay, D G, 1951, *Lancet*, 1, 284)

between the onset of an epidemic and the attainment of its peak in mortality, which may be due to an increased speed in dissemination of infection. It is only fair to point out that no definite correlation exists between the steepness of the curve and the subsequent height of mortality experienced at the peak.

An important circumstance concerning influenza mortality is the distribution in numbers of deaths in relation to the age of those concerned. This is the circumstance above all others which distinguishes the influenza pandemics of 1890 and of 1918 from other recorded outbreaks. For in these two pandemics the percentage of deaths in young adults 20 to 40 years of age increased out

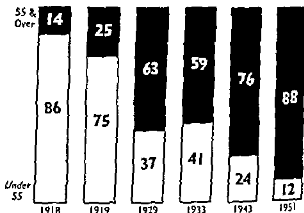


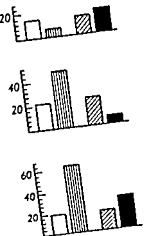
FIG. 74 —Age distribution of deaths from influenza in various epidemics Figures show percentages over and under 55 years of age.
(After Logan, W. P D, 1951, *Proc. Roy. Soc. Med*, 44, 793.)

of all proportion to those encountered in similar ages in ordinary epidemics. Greenwood (1920) considers that approximately 25 per cent of deaths from influenza in London in 1890 occurred in those aged 20–40. During the 1918 pandemic nearly 50 per cent of deaths from influenza occurred in those aged 20–40. Fig. 74 shows the percentage of deaths in those under 55 years of age to have been 86 in 1918, 75 in 1919, and 37 and 41 in 1929 and 1933 (Logan, 1951) The death rate in the epidemic of 1951 was borne almost wholly by those of 55 years of age and over, and the percentage of deaths in young adults reached a record low figure. Changes in age distribution since 1933 may, of course, have been due to the natural ageing of the population or to the more effective action of chemotherapeutic agents in younger persons But the reason for the ferocious onslaught of pandemic influenza of the type experienced in 1918 is

obscure. It is, indeed, this circumstance which has led various authorities to suggest that the 1918 pandemic was due to a type of influenza virus not experienced previously by the population. This 'new' virus could either have acquired exceptional virulence, or, by attacking a particular zone in the respiratory tract, have produced an unprecedented pathological effect on the lung, with resultant predisposition to bacterial complications. More will be said on this topic later.

An important way in which the effect of influenza epidemics upon the death-rate may be visualised, is by the record of deaths from acute primary and influenzal pneumonia. Fig 75 shows the age distribution and the numbers of deaths from pneumonia in Sheffield in the years 1947–51. The peak figures for deaths occurred in February 1951 and March 1949, both periods when influenza A was rife in the community. At these times almost all the mortality occurred in those of 65 years of age and over, and those between 45 and 65 contributed less than half the numbers furnished by the more elderly individuals. The absence of any increased numbers of deaths from pneumonia in children and young adults furnishes a vivid expression of the present benignity of influenza in this era of antibiotics and chemotherapy. In contrast, influenza is often the means of bringing to a halt the life of the aged and infirm.

Apart, however, from the mortality from pneumonia, which may frequently be ascribed to influenza as the primary cause, deaths from all causes rise during an influenza epidemic. Thus, deaths attributed to heart disease and to pulmonary tuberculosis both increase if the influenza epidemic is severe. Stocks (1935) considered that much of this general increase in mortality was the result of imperfect certification. The difficulty in arriving at an exact diagnosis in elderly people with pre-existing chronic disease of the lungs or heart and the rapidity with which they may succumb to influenza have not been sufficiently stressed in the past. During 1948 and 1949 an investigation was made by means of a questionnaire addressed to practitioners in the towns of the Sheffield region who recorded deaths from influenza. An analysis of 85 records during the influenza period in 1949 was compared with that of 29 records during the preceding year, when influenza was at a very low ebb (Stuart-Harris, Franks and Tyrrell, 1950). No obvious differences emerged, but it seemed clear from the notes supplied by practitioners that the illness frequently took the form of a sudden onset of pyrexia with a cough, either immediately or after an apparent lull, dyspnœa and general deterioration occurred, and the patient succumbed with



MAY
APRIL
MARCH
Number of Cases
10
10 20 30
10 20 30 40
20
20 40
20 40 60

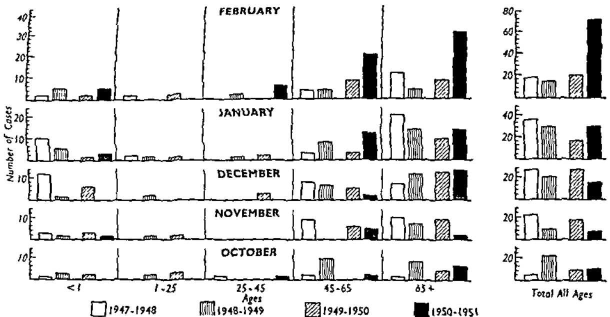


FIG 75.—Age distribution of deaths from pneumonia, 1947–51 (Sheffield)

Columns indicate the numbers of deaths from pneumonia arranged by age and by month in each of the four seasons beginning in October and ending in May

feeble rapid pulse or a bubbling rattling chest. In such cases, with death within three or four days from the onset of illness, it is by no means certain that pneumonic consolidation was present, and the condition could equally be ascribed to an acute bronchitis or bronchiolitis with profound toxæmia. In the 1951 epidemic a woman aged 69 died two days after admission to the ward in a desperately ill condition and with every appearance of pneumonic consolidation Influenza virus was recovered from the sputum, and though a pneumococcus was initially present in the sputum, this was absent from the lung at autopsy. There was pulmonary congestion, but no pneumonic consolidation. Another patient aged 55 was admitted during the epidemic in an extremely dyspnœic condition He was the subject of severe emphysema and chronic bronchitis, but had a localised tension pneumothorax, from which he died Influenza virus was recovered from the lung at autopsy. It seems likely that the pneumothorax had been caused by rupture of a bulla during a fit of coughing. Yet this mechanical death was initially caused by infection with the virus.

A series of 22 acute deaths occurring in Sheffield hospitals during the 1949 epidemic was investigated by test of sputum during life or of lung after death for influenza virus (Stuart-Harris, Franks and Tyrrell, 1950). The majority (17) were cases of pneumonia, and the *Staphylococcus aureus* was a frequent pathogen in the 8 cases yielding influenza virus by egg inoculation. The virus-negative cases sometimes yielded a *Staphylococcus aureus*, but more often a pneumococcus, an hæmophilus, or even a coliform organism was present in the lung at autopsy. Naturally, the lung flora may have been modified by chemotherapy, and thus the primary pathogen may have been extinguished. Among 3 patients with congestive cardiac failure who died relatively suddenly while in hospital, 2 yielded no virus but the third did This small series of tests indicated that influenza virus was more frequently demonstrated in fatal cases in association with the *Staphylococcus aureus* than any other pathogen Moreover, it clearly demonstrated the truth in the certification of death from pneumonia with influenza as a primary cause. Though this may occur more frequently in aged subjects with pre-existing chronic conditions, sudden death in the young adult or child does occur during an influenza epidemic And the recent work of Bowden and French (1951) in Australia has shown that influenza virus may be demonstrated to be the cause of death in some such instances

(iii) **Sporadic influenza.** The detection of sporadic cases of influenza virus infection is a bacteriological rather than a clinical

problem It is true that among the cases of acute respiratory disease occurring endemically in the population at all seasons of the year and in years when outbreaks of influenza do not occur, there are always some cases which could be diagnosed clinically as cases of influenza. Yet these almost invariably give negative results when tested either directly or serologically for evidence of influenza virus. The existence of true sporadic cases of influenza virus infection in the community in inter-epidemic periods has, however, been shown bacteriologically. The Commission on Acute Respiratory Diseases (1948) examined nearly 3,000 patients in Service hospitals with acute respiratory disease between 1942 and 1946 There were two periods of outbreaks of influenza, one of influenza A and one of influenza B, but, in addition, single cases or small groups of serologically positive cases were detected at other times, and, in all, these totalled 21 cases of influenza A and 24 cases of influenza B Small numbers of sporadic cases of influenza A and B were also detected among military personnel in Victoria, Australia, in 1943 by Beveridge and Williams (1944). Two sporadic cases of influenza A were detected in Sheffield during the winter 1947-48, when influenza virus was at a remarkably low level in the community. Moreover, an occasional case of influenza A or B is detected during an outbreak in which nearly all the other cases are serologically positive for the other virus infection Thus, in the epidemic among nurses at a Leicester hospital in 1949, the majority gave serological responses to influenza A. Yet one was serologically influenza B. Such experiences have frequently been recorded, and are again evidence that influenza can exist as a sporadic case However, the occurrence of a series of sporadic cases is no presage of an outbreak within a short space of time Its meaning is rather that the virus is still alive in the community and surviving the period of lean times, when the level of immunity is too high for rapid transfer of infection from one susceptible to the next

(iv) **The meaning of the 1918 pandemic.** The riddle of the epidemic of 1918-19 is a constant spur to all who are interested in research on influenza Although typing of the influenza viruses has now become an essential part of the epidemiological study of influenza, so far no correlation has been found between particular antigens and their clinical counterparts in terms of human disease Quite apart from the immense magnitude of the 1918 pandemic, two characters were exhibited which have not been encountered since One was the involvement of the age-groups 20-40 already mentioned, and the other was the remarkable incidence of lung complications

and high mortality in this group. There have been, it is true, minor outbreaks with unusual mortality, such as the Eskimo outbreak of 1949 (Nagler and co-authors, 1949) and the Liverpool epidemic of 1951. But the latter epidemic involved the older ages predominantly, and as the infection spread to other parts of England, no unusual features were encountered. Some believe (Burnet and Clark, 1942) that the essential novelty in 1918 was the biological or pathological property of the strain of virus. One has only to imagine that the virus had become more than usually adapted to growth in the human bronchioles or alveoli, to be able to explain the lung complications Young adults are distinguished from other members of the population by their vigorous over-reaction to many infections, and hence might be most affected by such a pneumotropic strain. Also, if the biological change had been linked to possession of a new antigen against which antibodies formed by previous experience of other antigens were incapable of reaction, then the young adults would represent virgin soil. The 1918 epidemic would thus resemble measles in the Fiji islanders (Brincker, 1938) which caused death particularly in young adults.

As Burnet (1951) has recently pointed out, the 1918 riddle is at this distance incapable of direct solution. We do not know the nature of the organism involved and may, indeed, never know, unless again overtaken by a similar calamity One hypothesis which was advanced by Laidlaw (1935) and Shope (1935) was that swine influenza, which appeared in the Middle West of the U.S.A. for the first time in 1918, may be a survival of the 1918 antigen in pigs. Attempts were made to check this hypothesis in 1936 by obtaining sera from islanders of St Helena and of Samoa, both areas which escaped the great pandemic of 1918. But, though the islanders had either none or a low level of antibodies to Shope's virus, a mild epidemic of influenza in St Helena in 1936 caused such antibodies to appear in these men and women, as it does in those resident in parts of the world afflicted in 1918. Thus the evidence did not support the hypothesis, but neither did it abolish it.

Meanwhile, the laboratory work on the influenza virus antigens has indicated the remarkable lability of the organism New strains have been developed in the laboratory by a sort of hybridisation (Burnet and Lind, 1951) with a novel combination of biological and antigenic properties If this can be done by human manipulations, it is certain that Nature can perform the task equally well, and probably much more efficiently The fact that the phenomenon exists is perhaps the best evidence that there is a known analogy for

the emergence of an apparently 'new' virus, and such may have been the responsible agent in 1918. Also, the antigenicity of influenza virus A strains in the last ten years strongly supports the view that 'new' viruses can emerge and become widely dispersed throughout the world within a relatively short period The so-called A prime viruses which now prevail appeared, apparently, in Australia in 1946, then in England and the U S A in 1947, and the older A viruses of the PR8 group have now been replaced As the A prime viruses produce the same biological effects as their earlier relatives, however, no comparable new epidemiological or clinical manifestations accompanied their emergence

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from its nadir of the summer months to coincide with the first sharp ... Hemisphere

from holidays and enter the new school term. ... ing of forms and classes will have changed, and new boys or girls have entered the school. Seven or ten days after the commencement of term, both in residential and non-residential schools, colds begin to occur, and the incidence of these swiftly climbs to a peak in about the third week. Usually there are few illnesses of a febrile character, and influenza is infrequently diagnosed In the general population at this time colds are rampant, and the occasional individual experiences an acute attack of bronchitis or pneumonia. When the fogs begin in November, the chronic bronchitic subjects begin to wheeze, and many experience acute exacerbation of their cough and sputum. The laboratory worker is now confronted by negative results. The respiratory infections yield no virus capable of cultivation by the available techniques, and serology has no better success During the rest of the time before Christmas general outbreaks of febrile respiratory disease in the community are unusual. Rarely an outbreak of influenza makes its appearance, as, for instance, in November 1943.

... usually in residential schools or in semi-isolated ... preceded by a ... t

and with pyrexia The possibility ... cases are clinically atypical, and may exhibit frank tonsillitis. In others laryngitis or a severe paroxysmal cough with substernal soreness suggesting tracheitis dominates the picture. Such are the febrile catarrhs which are unassociated with the influenza viruses In communities liable to periodic influx of newcomers they will occur in a succession of waves throughout the winter season. In the community in general they occur as a steady trickle of cases, and fail to achieve the intensity of incidence necessary for categorisation as an epidemic. In all such cases the laboratory usually fails to indicate the ætiological agent, and if evidence of influenza virus infection is sought, only sporadic cases are found.

As the winter progresses, the post-Christmas period is almost always the occasion for a general wave of febrile respiratory infections in the community Colds are active as well, as will be evident in schools soon after the reassembly of the scholars for the Easter term Often, however, the colds are cloaked by the more serious pyrexial illnesses which are the special province of the influenza viruses. If,

indeed, the viruses are about, then this is the time when the general population will be exhibiting outbreaks accompanied by a rise in mortality from all causes, and especially from influenza and pneumonia. If the viruses are not prevalent, then the wave of febrile infections will soon pass away, and the expected epidemic will not materialise. Pneumonia, however, is at a higher level now than in the autumn, and will maintain a plateau of incidence without a peak if no sharp outbreak of influenza develops.

The arrival of Easter may bring a slackening of the endemic respiratory infections, and summer outbreaks are increasingly improbable as the temperature rises. Very occasionally, however, localised outbreaks of febrile respiratory disease may occur in the late spring or early summer, and sometimes these may represent a summer epidemic of influenza virus infection. No general outbreak is likely in the population at such times.

The above picture is perhaps imaginative rather than factual, but it may serve to indicate the great complexity of events to the man-in-the-street observer. The problem of the febrile cases of respiratory disease is a formidable one for the diagnostician. If the latter is actually responsible for the health of a group of servicemen in a recruiting centre, he may be quite unaware of any distinction when the influenza virus actually arrives in his group, for the febrile catarrhs are clinically similar to the influenzas. Yet there are some clinical differences between the two groups of cases, and it is therefore worth while analysing the catarrhs in more detail.

Let us first consider the situation as it was seen in a service establishment in Great Britain during the second world war.

Outbreaks of respiratory disease at an infantry training centre.

Fig 76 represents the total weekly numbers of respiratory infections at a particular infantry training centre in the Eastern Counties of England between December 1942 and March 1944. The same medical officer saw all the fresh cases of respiratory disease during this period, and the graph has been constructed from his diagnoses. Only the total figure of weekly cases of reported febrile and afebrile disease, including the common cold, pharyngitis, tonsillitis, laryngitis, sinusitis, bronchitis, influenza and pneumonia, is given. The majority of cases were febrile. The attack-rate was not calculated because, as the graph shows, recruits were entering usually once or twice a month in batches from 50 to 300 at a time. The population of the centre fluctuated around an average of 1,500–2,000. The men

entering this centre stayed for a period of six weeks in the two companies forming the corps training group. A small staff of relatively permanent establishment maintained the training and administration, and the recruits entered a company as a large batch, which replaced those men leaving in the previous week. Never-

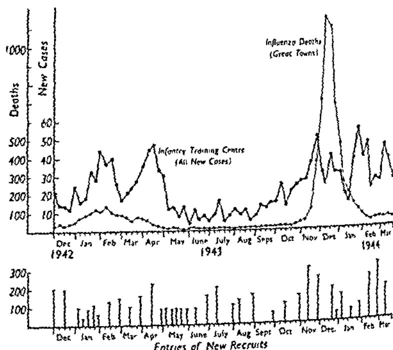


FIG. 76.—Weekly respiratory infection at an infantry training centre, 1942–44

Thick line represents weekly numbers of all respiratory infections

Thin line based on weekly influenza deaths in the Great Towns of England and Wales.

The population at the centre was varying continually because of the entry of new recruits (lower figure). Similar numbers left the centre a few days previously.

theless, the centre had common mess-rooms and recreation halls, though the individual companies had separate barracks.

As a background to the curve derived from the cases of respiratory [illegible] in the Great [illegible]. This line [illegible] epidemic, reached a peak in November 1943, during the [illegible] and a smaller plateau was exhibited in January 1943, when a minor outbreak of influenza B occurred. The infantry training centre experienced at least four waves of respiratory infection, with peaks

in January, March and November 1943 and January 1944. As the graph shows, the outbreaks of January and November 1943 were probably due to influenza virus infection, but the other outbreaks occurred when no parallel country-wide epidemic was in progress It is extremely probable that if cases in these outbreaks had been tested for influenza virus none would have been found. No tests were, in fact, made prior to January 1945

Fig 77 shows the experience at this same training centre during the later months of 1944 and early 1945 There was a sharp,

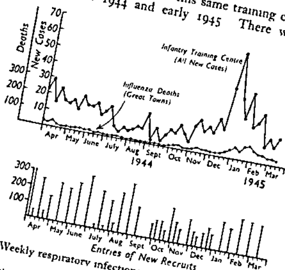


Fig 77 —Weekly respiratory infections at an infantry training centre, 1944–45

Explosive outbreak of febrile catarrh in January 1945 at a time when influenza deaths were less than 100 per week

most explosive outbreak in January 1945 Influenza was then at a low level in the general community Sera from 40 patients were tested for influenza virus antibodies by the Hirst test, and the results in 38 were negative Two were apparently cases of influenza B The remainder were cases of acute respiratory disease of varying grades of severity, and the outbreak was one of febrile catarrh How many of the earlier waves at this training centre were of similar character is a matter for speculation, but the probability is that the majority were not due to the influenza viruses

This experience was paralleled during the war by other training centres in Great Britain and in the training battalions in the U.S.A The Commission on Acute Respiratory Diseases (1946a)

carried out extensive investigations at Fort Bragg between November 1942 and January 1945. Each winter season there were large outbreaks of respiratory disease, yet tests for influenza virus infection gave positive results only during the influenza A epidemic of the winter of 1943 and in occasional sporadic instances apart from this. The American workers found that nearly all the cases of non-influenzal respiratory disease occurred among the recruits, there being an incidence ten-fold greater in the recruits than in seasoned men in the winter seasons. The British outbreak in January 1945 which has already been described, and which was tested for influenza with negative results, was also largely a recruit disease. The highest weekly attack-rate occurred in the youngest recruits of less than six weeks service in the primary training wing, the next highest in the recruits of more than six weeks but less than three months service in the corps training unit, and hardly any cases at all occurred amongst the permanent staff of seasoned men. The weekly attack-rate in the primary training wing reached the figure of 5·8 per cent at the peak, whereas the figure for the corps training units did not exceed 4 per cent per week at any time. Because the latter units were larger than the former, they did in fact provide the bulk of the cases. Clearly the initial few weeks of experience of Army life in some way furnish a most suitable breeding-ground for the febrile catarrhs. Once an outbreak develops, the fact that it is largely limited to recruits also suggests that immunity to these infections develops, and this is no doubt a part of the seasoning process traditionally regarded as part and parcel of Army life. The reason for the periodic waves in the training centres is probably related to the intake of recruits. At Fort Bragg it was observed that febrile catarrh usually developed in various battalions within the first month after the arrival of recruits, but in other military establishments which received a constant flow of recruits there was less tendency to such a periodic pattern of outbreaks. Experience at the British Infantry Training Centre shown in Figs. 75 and 76 did not suggest any close relationship between outbreaks and the arrival of recruits, perhaps because the majority of the recruits were immediately segregated into individual companies.

Febrile catarrh in the general population

Information concerning the behaviour of respiratory diseases in the community as a whole is not precise, though there is no need to minimise its numerical importance. It was at one time hoped that morbidity surveys by social workers would give information on this

point, but the data recorded are almost worthless from the standpoint of differentiating types of illnesses as is necessary in connection with the present problem Surveys made in industry indicate the frequency of acute respiratory disease of a character more serious than that of colds But it is not at all clear whether such disease is to be regarded as the civilian equivalent of the Army disease described above Usually certification of such cases is based on the term 'bronchitis'. It is certainly the case, as in the service epidemics already described, that the winter season is the time for increased incidence, and presumably this is in part due to climatic influences Apart from schools and service establishments, febrile respiratory disease unassociated with the influenza viruses is rarely accompanied by an attack-rate in the general community sufficient to cause an actual outbreak, but information is not precise, and outbreaks may occur in the public which for one reason or another have not received attention. This is a relatively unprobed field, and one in which research is greatly needed Until an ætiological agent has been defined, however, it is unwise to expect much progress

The age-distribution of febrile catarrh is masked by the influence of factors such as those indicated by the term 'recruit infection'. It would be expected, however, unless immunity is temporary, that children [illegible]
subjects. [illegible]
areas. [illegible]
by Dr. Pickles among the villages in Wensleydale during three years. In 1943, 61 cases were recorded The majority occurred in January or November, and were almost certainly accounted for by influenza B and A, respectively. The two years 1942 and 1948 yielded 31 and 34 cases, respectively They are quoted deliberately because of an absence of recorded recovery of influenza viruses in Great Britain in these years. The cases came within the general group of febrile catarrh as already defined, but excluded cases of tonsillitis As the Table shows, there is no appreciable difference between the age distributions for the influenza year of 1943 and the non-influenzal years of 1942 and 1948

Apart from such figures, there are no data concerning the frequency of febrile catarrh among people living in their own homes However, more than one observer has commented recently upon the general low level of streptococcal infection in cases dubbed 'tonsillitis'. It is more than likely that the febrile sore throat endemic in the population, excluding that due to streptococcal infection, is a manifestation of febrile catarrh So also it is likely that

TABLE 14

Age-incidence of Influenza and Febrile Catarrh in Wensleydale

Year.	Probable nature of infection	Years of age					Total.
		10.	10–19	20–40	40–60	Over 60	
1943	Influenza A / Influenza B	20 (32·8)*	9 (14·7)	10 (16·4)	10 (16·4)	12 (19·7)	61
1942–1948	Unknown	19 (29·2)	5 (7·7)	18 (27·7)	15 (23·0)	8 (12·3)	65

* Percentage of total numbers in brackets
(Constructed from data kindly supplied by Dr W. N. Pickles of Aysgarth.)

many cases of acute bronchitis fall into this ætiological group rather than into the group of the influenzas.

Clinical patterns of febrile catarrh

The earliest published account of febrile catarrh in Britain (Stuart-Harris, Andrewes and Smith, 1938) was followed in 1946 and 1947 by more comprehensive resports from the American Commission on Acute Respiratory Diseases (1947*b*). It must be remembered that the earlier outbreaks studied in Britain in 1936 occurred long before influenza virus B had been recovered in the laboratory, and therefore there was only proof that influenza virus A was not concerned The American cases were, however, tested adequately against both influenza viruses, as were the cases at the infantry training centre in Britain in 1945 which were described above. The epidemics studied in 1936 gave then the impression of a variable clinical picture, as though there were several conditions occurring side by side. Uncomplicated cases comprised those with an influenza-like illness or else with frank tonsillitis, including cases with a faucial exudate Complicated cases exhibited a basal bronchitis or else pneumonia Relatively few patients were X-rayed The group of patients studied by the Commission on Acute Respiratory Diseases during the three-year study at Fort Bragg from 1942 to 1945 were classified as cases of influenza virus infection, cases with pneumonia (either bacterial or atypical), cases with exudative tonsillitis and pharyngitis (some with and others without evidence of streptococcal infection), and finally A.R.D (febrile catarrh) The last-named furnished between 75 and 90 per cent of all patients with respiratory disease admitted to hospital. The resemblance between the British and American experience was thus reasonably good, and suggests that both groups were studying similar conditions.

The difficulty in giving a clinical account of febrile catarrh is that, although different clinical patterns occur within the group, there is no certain knowledge that these represent different entities from the aetiological standpoint. This is most clearly seen in relation to the syndrome of atypical pneumonia. Routine radiological examination of the chest in cases of febrile catarrh shows abnormalities in a small proportion of instances. At Fort Bragg about 10 per cent of cases of respiratory disease at all seasons and degrees of epidemicity revealed X-ray changes in the lungs. Such were described as atypical pneumonia. This constant ratio of one in ten suggested a relationship between such cases and the outnumbering cases of febrile catarrh. Nevertheless, the experiments on human volunteers carried out by the Commission on Acute Respiratory Diseases (1946b and 1947c) did not confirm that the conditions of atypical pneumonia and acute respiratory disease were due to the same agent. However, atypical pneumonia is a complex syndrome, and it seems best to deal with its clinical manifestations separately from those of the other members of the febrile catarrh group.

The American Commission also separated cases with exudative tonsillitis or pharyngitis from the other patients, yet there seems no valid reason for this distinction until more is known concerning their respective aetiology. After all, the words febrile catarrh were used deliberately to indicate that, in contrast to influenza, this condition presents an exudative or catarrhal aspect. The following two cases (20 and 21) illustrate febrile catarrh occurring during the outbreak at the Army training centre in 1945 already described. Case 20 represents an influenza-like attack. Case 21 was a case of exudative pharyngitis.

Case 20. *Uncomplicated febrile catarrh*

P. B., aged 18, first noticed hot and cold feelings on the 2nd January 1945. On the 3rd January he had a slight cold and sore throat. He felt ill and shivery. He reported his illness on the 4th January, and complained chiefly of cough. Headache was trivial, but there had been slight abdominal pain and pains in the thighs. His voice had become hoarse, but the sore throat was no worse.

Temperature was 100.4° rising to 102.8° F., pulse 104, respirations normal (Fig. 78). His face was flushed and slightly cyanosed. The eyes were glistening. The pharynx was slightly red, but there was no exudate. Rhonchi were heard at both bases. The temperature remained elevated until the morning of the 7th. On the 8th January he still had a dry cough and the voice was hoarse. There were rales at the right base, but an X-ray examination of the chest showed no abnormality. Convalescence thereafter was uninterrupted. Acute and convalescent samples of serum showed no rise of titre against influenza viruses A and B by the Hirst test.

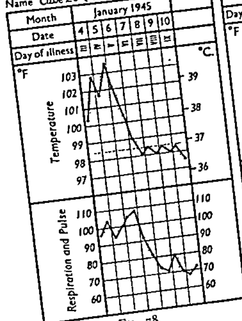


FIG 78

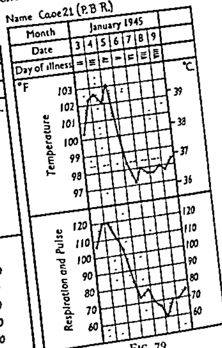


FIG. 79

CASE 21. *Febrile catarrh with exudative pharyngitis.*

P. B R., aged 19, had been in the Army for one week only. He lost his appetite on the 31st December 1944, but was otherwise well. On the 2nd January, after a long march, he felt shivery and hot. His head ached. On the 3rd January he was admitted with a temperature of 100 4° rising to 102 2° F. (Fig 79) He still had a headache, and now a cough The nose was blocked On the 4th January fever continued. The throat now showed an exudate of slimy mucopus on the posterior pharyngeal wall where adenoid tissue was swollen. On the 5th, fever began to lessen. The throat remained the same, with exudate extending on to the pillars of the fauces Cervical lymph nodes were not enlarged. There were no abnormal signs in the chest Epistaxis occurred on the 6th January. An X-ray examination of the chest on the 7th January showed no abnormality The fauces were still injected, and the nose was still stuffy Convalescence was soon established.

Throat-swabs taken on the 4th January showed a few hæmolytic colonies, but these yielded only an hæmophilus on sub-culture Again on the 5th January no hæmolytic streptococci were found by throat-swab culture Acute and convalescent samples of serum showed no rise in titre against influenza virus A and B by the Hirst test

The next patients—Cases 22 and 23—illustrate cases of febrile catarrh seen in January 1939 in an outbreak at R A F. and Naval

training establishments shortly before the occurrence of influenza virus A and B infection.

CASE 22 *Severe pharyngitis and laryngitis*

E F., aged 17, had been serving in the R.A F. for three months. On the 21st January he became giddy, developed a headache and felt shivery. He awoke on the 22nd with cough and sore throat There was still headache The cough was dry, but hurt his throat and substernal region His voice

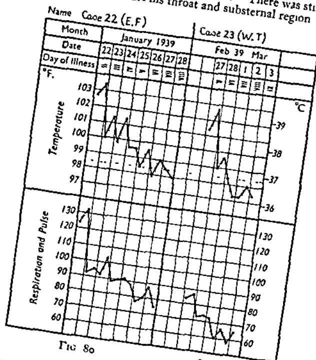


Fig 80

Fig 81

began to be hoarse He vomited once On admission the temperature was 103 4° F, pulse 130 The next day the temperature had fallen, but he still felt ill, with continued coughing and a very hoarse voice The nose was blocked, but did not run Appetite was bad On examination on the 23rd January he was pale with slight duskiness of the lips The conjunctivæ glistened, the tongue showed a brownish fur The pharynx was only slightly injected, but there were whitish spots of exudate on the lateral and posterior pharyngeal walls Cervical glands were a little enlarged, but not tender The chest was pigeon-shaped and exhibited generalised rhonchi

His condition remained much the same until the 27th, when the temperature fell Cough and sore throat continued for at least a further

k. He was aphonic on the 1st February, but the voice began to return
veek later. At no time were hæmolytic streptococci recovered from
roat-swabs. Serological tests for influenza virus infection were negative.

ASE 23. *Febrile catarrh with bronchiolitis.*

W. T., aged 20, had a cold and cough in January 1939, but was well until
e 13th February, when the cough was worse. On the 23rd there was a
ull ache beneath the left scapula, not made worse by breathing. There
vas no fever until the 27th, when he was still coughing, complained of
eadache and felt faint on walking. The nose was obstructed, but not
discharging; the throat was a little sore. Temperature was 101.4° rising
to 102.6° F., pulse 80–90 (Fig. 81). He complained of backache and of
pain in the centre of the chest, hurting him when he breathed. He was
coughing frequently in a paroxysmal manner, appeared flushed with
circumoral pallor and had glistening eyes. The tongue was coated, the
fauces were intensely red, with slight swelling of the tonsils but no exudate.
The nose was blocked, the voice husky, and both bases exhibited fine
râles and diminished breath-sounds. The fever was short-lived, but
added sounds continued in the chest, though X-ray was within normal
limits. Greenish mucopurulent sputum was raised on the 1st March.
The voice was not hoarse, the fauces showed only slight enlargement of
the adenoid tissue. Convalescence was fully established by the 7th March.
The leucocyte count was 10,000 per cu. mm. on the 1st March and 8,800
on the 3rd. Serological tests for influenza virus infection were negative.

The course of illness in febrile catarrh

The incubation period is unknown and is difficult to surmise, because the onset of illness is as often insidious as abrupt, and premonitory symptoms such as cough, coryza or malaise may be present for several days before the commencement of fever. The temperature then rises abruptly, and the patient complains of shiveriness, headache, loss of appetite and a feeling of illness. Respiratory tract symptoms are prominent at the earliest stage, cough is dry but frequent and irritating, the throat is frequently sore, the nose is blocked or running, and the voice loses its tone. On examination, on the first or second day of fever, the patient is moderately ill with facial flush and glistening, slightly injected conjunctivæ. The nose is frequently blocked and sneezing is common. The tongue is usually dirty, with whitish fur. The fauces present a strikingly flushed or injected appearance, perhaps even with minute hæmorrhages on the soft palate. An exudate is present on the tonsils or on swollen adenoid tissue on the posterior pharyngeal wall in about one-quarter of the cases. It is, however, uncommon for such exudate to be follicular or confluent, as in the case of hæmolytic streptococcus infection. It presents rather an appearance suggesting a post-nasal extension of loose blebs of mucus. In structure it is

mucopurulent or flocculent, and it may form a slimy coating covering the tonsils. According to the American observers, it is often discrete and whitish. Unlike the findings in streptococcal cases, the cervical lymph-nodes are either normal or only slightly enlarged in the submandibular area. The chest presents scattered râles or rhonchi in roughly one-third of all patients and is normal in the remainder.

The fever lasts for two to three days on the average from the day of onset, and may be as high as 103° or 104° F for a brief period. At this stage the pulse is usually elevated, but not disproportionately to the fever. Respirations are normal. The cough frequently dominates the illness, and is of the paroxysmal and irritating variety common to upper respiratory tract infections involving the trachea. Pain on coughing is present in about one-third of patients, and is usually felt as a substernal soreness rather than as a lateral pain of pleural type. As the disease progresses, sputum may appear, but this is not usually abundant, and presents a sticky, mucopurulent appearance. Hæmoptysis is uncommon except for slight blood-streaking in those with the more severe degrees of respiratory tract involvement. In such patients the voice is usually hoarse or reduced to a whisper, and added sounds are present in the chest. X-ray examination of the chest shows no abnormality in the majority of cases. *In others the picture is of an atypical pneumonia or of a segmental area of collapse at one or other lung base (see Chapter 8).* The presence of such radiological abnormality may be difficult to evaluate in subjects with a history of bronchitis in childhood or of chronic cough with sputum.

The blood count is undistinctive. Neither a leucocytosis nor a leucopenia is present, and the range of 6,000–10,000 leucocytes per cu mm covers merely that of the normal subject.

The pathological condition underlying febrile catarrh is unknown, but the pharynx, larynx and trachea obviously bear the main brunt of the attack. To decide whether or not there are distinctive changes compared with those of influenza virus infection, it will be necessary to await recovery of the virus agent and study of its effects in experimental animals.

Comparison of febrile catarrh and influenza

It will be obvious that febrile catarrh can justly be described as an influenza-like illness, and in view of the variable clinical picture of influenza, clinical differentiation is very difficult. This may be readily seen by reference to Table 15, which gives the percentage frequency of symptoms in the two conditions.

TABLE 15

Frequency of Various Symptoms in Febrile Catarrh and Influenza

Symptoms	Febrile catarrh.		American A.R.D.*	Influenza	
	28 cases, 1936	17 cases, 1945.	113 cases, 1942–45	Infl. A, 84 cases, 1937.	Infl. B, 24 cases, 1943
(a) *Respiratory*					
Cough	86	88	85	71	92
Sore throat	80	70	69	43	42
Nasal symptoms	70	70	60	73	66
Expectoration	50	23	54	31	24
Hoarse voice	40	40	75	6	12
Pain in chest	40	10	48	24	33
(b) *Constitutional*					
Malaise	82	23	53	91	80
Shivering	70	53	69	74	82
Anorexia	70	23	55	77	79
Headache	64	76	65	87	83
Dizziness	64	23	—	62	58
Muscular pains	53	30	—	51	75
Sweating	50	—	—	31	91
Insomnia	40	17	—	32	12
Average duration of fever	3 days	?	2–3 days	3 6 days	3 days
Abnormal signs in chest	33	23	27	23	18

Figures refer in each group to the percentage incidence of the symptom
* Commission on Acute Respiratory Diseases (1948)

There is no doubt that the degree of sore throat and hoarse voice and frequency of the irritating, painful cough of febrile catarrh presents a contrast with influenza virus infection. If an exudate is present on the throat, then influenza is unlikely. However, the absence of any of these symptoms or signs is still compatible with febrile catarrh, and such patients are clinically indistinguishable from cases of influenza. The frequency of abnormal signs in the chest (about 30 per cent) in febrile catarrh is not greatly different from that in cases of influenza. Radiological abnormalities are probably slightly commoner in febrile catarrh. The leucocyte counts do not distinguish the two conditions.

Thus confronted by two patients, one with febrile catarrh and the other with influenza, the clinician would be likely to err. If, however, a dozen or so of patients from outbreaks of the two conditions were examined, a greater chance exists of clinical differentiation. It is obvious that ultimate appeal to the laboratory is necessary for certain diagnosis to be achieved.

Differential diagnosis from streptococcal infection

The second most important differential diagnosis of febrile catarrh is that of streptococcus sore throat. These conditions tend to occur in much the same populations, and streptococcal infection usually occurs at least sporadically whenever respiratory tract infections are rampant. The differential diagnosis is particularly difficult when an exudate is present on the throat. Both conditions cause short fevers, with headache, shivering and malaise. But cough, nasal symptoms and hoarse voice are prominent in febrile catarrh, whereas the chief respiratory symptom of streptococcal infection is sore throat. There is pharyngeal injection in both conditions, but this is usually more intense, and often accompanied by œdema in streptococcal infection. The exudate of streptococcal infection is either follicular or coalescent, but the colour is yellowish-white contrasting with the greyish, slimy exudate situated over the tonsils or adenoid tissue in febrile catarrh. The cervical lymph nodes, particularly in the sub-mandibular area, are enlarged and tender in streptococcal infection, but are not usually enlarged in febrile catarrh. Finally, a poly-morphonuclear leucocytosis is frequent in streptococcal infection and the total count averages 14,000 per cu mm. Cultivation of a throat-swab will usually make clear the diagnosis of streptococcal infection, though the detection of only one or two colonies of hæmolytic streptococci on a blood-plate is not adequate for proof that this is the causative organism because of the existence of streptococcal carriers.

The ætiology of febrile catarrh

The causative organism of febrile catarrh has not yet been demonstrated. Bacteriological studies made in 1936 were not comprehensive, but failed to indicate any constant bacterium in the naso-pharynx of cases during the acute stage. Detailed bacteriological observations made by the Commission on Acute Respiratory Diseases (1947*d*) showed no consistent alteration of the flora in control individuals during febrile catarrh compared with the nasopharyngeal flora. Moreover, the carrier rates of hæmolytic streptococci, *Staphylococcus aureus*, pneumococci, *Hæmophilus influenzæ* and *Hæmophilus hæmolyticus* showed no correlation with the prevalence of minor respiratory disease in the community.

Attempted cultivation of virus agents from the gargling from cases of febrile catarrh either by ferret inoculation or by the use of hens' eggs has given negative results. The only indication that filterable

agents are ætiologically concerned has been the result of extensive experiments on human volunteers carried out by the Commission on Acute Respiratory Diseases (1947*c*). Sterile filtrates derived from the pooled nasopharyngeal secretions collected from a single donor with typical febrile catarrh were inoculated into human volunteers by causing them to inspire atomised droplets. Twelve of a group of 14 volunteers developed illnesses described as 'minor respiratory illness' after an average incubation period of five or six days The induced disease was only mildly febrile (maximum temperature 99·8° F.); there was a sore throat, sneezing, nasal obstruction or discharge; hoarseness of the voice and cough developed in half the subjects None showed pharyngeal exudate The volunteers appeared immune to a reinoculation of the same material twenty-one days later, though at the same time other subjects who had received material twenty-five days previously from a case of common cold developed minor respiratory illnesses similar to those observed in the first group of volunteers. The inoculations of material from the A.R.D. case did not render the original volunteers immune to the effects of material from a common cold, which produced in them, as in normal individuals, nasal symptoms after a short incubation period.

The conclusions arising from these experiments were firstly that febrile catarrh is ætiologically unrelated to the causal agent of the common cold and secondly that it is a disease with a rather longer incubation period than either the common cold or influenza. Much hinges on the vital question as to whether the induced minor respiratory illness really was the same condition as naturally encountered febrile catarrh. It certainly lacked much of the severity of the illness exhibited by the 'donor' patient Fever was unconvincing and symptoms were mild However, the clinical picture of an illness dominated by a sore throat rather than by a cold does not suggest that the minor respiratory illnesses were simple colds Again, the cross-immunity tests suggested that the transmitted disease 'bred true' produced immunity against its own causative agent and failed to immunize against the common cold. None of the volunteers developing minor respiratory illnesses underwent a significant change in the bacterial flora of the nasopharynx or in the leucocyte count. Nor did antibodies to the influenza viruses develop It is therefore unlikely that the transmitted disease was a bacterial or an influenza virus infection. On the whole, therefore, the evidence seems good that a febrile catarrh was transmitted, and that the clinical differences from the natural disease were explained partly by the fact that the experiments were conducted in the summer time,

and possibly also because of a state of partial resistance on behalf of the volunteers. It is difficult to visualise much further progress in knowledge of the ætiology of febrile catarrh by experiments conducted only on human volunteers

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CHAPTER 8

THE SYNDROME OF ATYPICAL PNEUMONIA

THE existence of a form of pneumonia clinically distinct from ordinary bacterial lobar or bronchopneumonia has been recognised for at least fifteen years The use of sulphonamides and then of penicillin assisted in this recognition, though in the U.S A. the era of treatment of pneumonia with specific sera had awakened interest at an even earlier date in cases apparently different clinically and ætiologically from lobar pneumonia and termed for this reason atypical pneumonia (Cole, 1936). At the present time there has been first of all an apparent change in the clinical picture of ordinary pneumococcal pneumonia The age incidence has altered; there are fewer cases in young adults and more in elderly subjects, in whom the illness is less clear-cut and the physical signs less frank. Moreover, some patients do not yield bacteria in the sputum cultivatable by ordinary means or by mouse inoculation. The results in cases of pneumonia studied in Sheffield in the years when influenza epidemics did not occur have already been described (Chapter 4). No pathogenic bacteria were identified in 25 of 130 cases (19 per cent) of verified consolidation of the lungs examined bacteriologically before chemotherapy was begun There is now no second chance in this bacteriological study because, if chemotherapy is effective, as usually happens, organisms such as pneumococci disappear rapidly from the sputum In many instances these cases of pneumonia in whom the cause is unidentified respond normally to chemotherapy. Such may be regarded as being of probable bacterial origin in whom for some reason the organism has not been present initially in the sputum in large enough numbers for demonstration by the available techniques. In other cases therapy is less successful, and further study may reveal that the cause is a *Staphylococcus pyogenes* or the tubercle bacillus, and the clinical course in such cases is clearly different from that of ordinary pneumococcal pneumonia But in yet other cases the unresponsive character of the pneumonia to chemotherapy with sulphonamides or penicillin raises the possibility that the case is one of atypical pneumonia due to a virus or rickettsial agent

There is, however, an entirely different mode of presentation of cases of atypical pneumonia which is probably the chief way in which cases are encountered in Britain at present. This is by the dis-

covery of widespread radiological changes in the lungs in cases previously diagnosed as pyrexia of unknown origin, influenza, bronchitis or minor respiratory infection. This was the way in which Gallagher reported a series of sporadic cases among preparatory schoolboys in Pennsylvania in 1934 He described the condition as 'pneumonitis', and in a later series in schoolboys in Massachusetts in 1939 and 1940 (Gallagher, 1940) thought the condition was an infectious disease. The use of radiology in the investigation of cases of acute respiratory disease in recruits and other servicemen also revealed the existence of unsuspected lung lesions (Bowen, 1935; Allen, 1936) It was not until the second world war, however, that a clinical picture associated with similar radiological changes was encountered at all frequently, and from 1942 onwards outbreaks occurred in American troops both in the U S A and elsewhere. Though sporadic cases were also identified in Britain, there were no outbreaks in British forces until the year 1944, when Allied troops in Italy suffered from explosive epidemics The use of the name 'primary atypical pneumonia' by American authors displaced the earlier word 'pneumonitis', and extensive investigations pursued by Eaton and others (1944) and by the Commission on Acute Respiratory Diseases indicated that a virus agent was probably concerned. However, the explosive outbreaks in Italy and elsewhere were soon identified (Robbins and co-authors, 1946) as a manifestation of Q fever, the causative agent of which is a rickettsia (*R burneti*). It was thus clear that more than one agent could produce a similar clinical picture, and this is the reason for describing atypical pneumonia as a syndrome Meanwhile, serological investigations of cases of atypical pneumonia in Great Britain and in the U S A indicated that infection by the psittacosis and ornithosis group of viruses was detectable in only a minor percentage of cases The majority of cases failed to yield any identifiable virus, though successful transmission to human volunteers with filtered material was obtained by the Commission on Acute Respiratory Diseases (1946) It is such cases of atypical pneumonia of unknown origin to which the name primary atypical pneumonia may still be given

Primary atypical pneumonia of unknown ætiology

This can be defined as a febrile disorder affecting the respiratory tract with a symptomatology similar to that of influenza or of febrile catarrh. Radiological changes can be demonstrated in the lungs, and there is no therapeutic response to penicillin or the sulphonamides

Epidemiology. Primary atypical pneumonia is commoner in young adults than in either infants or the elderly. As encountered in civilian practice, it appears to have many of the features of an infectious disease. Thus family outbreaks have often been described, and in affected families a protracted incubation period of five to nineteen days with a mean of 12·7 days is discernible (Jordan, 1949) Children are affected in these family outbreaks, and school epidemics certainly occur. Apart from the outbreaks described by Gallagher, that occurring in a residential school in Britain in 1942, and described by Herxheimer and McMillan (1942), may be quoted Extended family outbreaks have also been recorded in Scandinavia (Hogeman, 1948) and in Ireland (Alton and Hickey, 1948). There are good grounds for believing that these were outbreaks of primary atypical pneumonia because of the development in the affected persons of a high titre of agglutinins for human red cells in the cold. Such cold agglutinins were recognised as a frequent finding in the convalescent serum of service patients with primary atypical pneumonia during the war years, and are not characteristic of Q fever or psittacosis

As seen in servicemen, primary atypical pneumonia appears sporadically, yet increasing in incidence during outbreaks of febrile catarrh. An incidence of roughly one to ten cases of febrile catarrh was recorded by the Commission on Acute Respiratory Diseases (1944*a*), and this proportion was maintained whatever the level of incidence of febrile catarrh. A body of opinion also supports the view that cases of bronchitis or of bronchiolitis with negative radiological findings yet occurring in close contacts of cases of primary atypical pneumonia may in fact be due to the same ætiological agent. No evidence in support of this view can be accepted until the hypothetical agent has been discovered It may be said, however, that it is difficult to discern any chain of infection in servicemen between cases of primary atypical pneumonia as has been demonstrated in family outbreaks.

Clinical features. The onset of illness is usually insidious, and lacks the abruptness and the pleural pain so common in bacterial pneumonia. Instead, a cold, cough or sore throat may suggest a minor respiratory illness until headache, malaise and shivering usher in the febrile phase There is now a dry cough, which may be frequent and irritating It is often painless, but in many patients some form of chest pain occurs on coughing, either substernally or at the costal margin. As the disease progresses, sputum appears, and is usually sticky and mucopurulent Occasionally it is blood-streaked. The fever, which lasts about a week or ten days, is lower

than the fever of lobar pneumonia and may pursue an intermittent or remittent course. The patient looks moderately ill. Cyanosis, if present, is slight and dyspnœa is exceptional. Suffusion of the eyes and evidence of nasal obstruction are common. The pharynx is injected, but has no exudate. The commonest physical signs are those in the chest, where localised areas of sticky râles with diminished breath-sounds occur over one or other lung base. Râles may be heard only after coughing or deep inspiration. On the other hand, some patients exhibit diffuse râles in other areas, suggesting a general bronchitis. Dullness is minimal, and bronchial breathing does not usually occur. The pleura usually escapes involvement, so that friction or the presence of fluid is exceptional. There is considerable variation in the percentage frequency of symptoms and signs recorded in the literature, as may be seen by reference to Tables 16 and 17.

TABLE 16

Percentage Incidence of Symptoms in Primary Atypical Pneumonia

			Commission on Acute Respiratory Diseases, 1944 (69 cases)	Curnen and co-authors, 1945 (101 cases)
Onset	Gradual		74	73
	Sudden		26	27
Constitutional symptoms	Headache		78	65
	Malaise		77	61
	Chilliness		75	59
	Anorexia		—	35
	Nausea		—	28
	Generalised aches		—	28
	Vomiting		—	24
Respiratory symptoms	Cough		99	98
	Sputum		—	82
	Non-bloody		52	—
	Bloody		12	25
	Coryza		41	—
	Sore throat		36	30
	Chest pain	Substernal	26	24
		Lateral	18	15
	Epistaxis		—	15
	Dyspnœa		—	5

The course of the disease usually occupies a period of two to three weeks, but radiological changes may persist for a longer period. The condition is only rarely fatal.

The radiological changes are usually more extensive than the physical signs suggest, but again variation is observed, and there is

TABLE 17

Physical Signs in Primary Atypical Pneumonia (Percentage Incidence)

	Commission's series.	Curnen and others.
Degree of illness.		
Acutely ill	12	—
Moderately ill	74	—
Fever	81	95
Nasal congestion	28	57
Faucial injection	55	69 (pharyngitis)
Suffusion of eyes	20	—
Cervical adenopathy	—	24
Signs in the chest.		
Dullness	41	54
Altered breath-sounds	4	70
Râles	93	93
Rhonchi	43	—
Friction	—	7
Fluid	—	1
Bradycardia	—	68
Tachycardia	—	8
Tachypnœa	—	13
Cyanosis	—	11
Signs in the C N S	—	6
Palpable spleen	—	1

widespread controversy concerning their interpretation In Gallagher's original descriptions (1940) an opacity originated at the hilum and spread fanwise along the main bronchus to apex or base. Usually one, but occasionally two or three lobes were involved. In American servicemen the opacity is sometimes described as beginning in an isolated area out in the lung field, but more usually as an enlargement of the hilum from which the opacity extends towards the periphery The density is never as great as in lobar pneumonia, and is either granular or homogeneous Although uniform opacity is probably the common finding, other observers describe a mottled or even a miliary pattern. Frequently the involvement is of only part of a lobe, extending usually from an enlarged hilar shadow. Lower lobes are involved more frequently than the upper, but either lower lobes are equally affected. Such radiological changes may persist for days or weeks, clearing usually being from the periphery towards the hilum. The average time taken for resolution is two to three weeks, but enlarged hilar shadows may persist for several weeks.

It will be at once understood that the differential diagnosis of such radiological appearances requires good X-ray technique, and lateral

radiograms are necessary as well as postero-anterior views A thin layer of fluid or a collapsed lobe may, for instance, produce identical radiological appearances to those of atypical pneumonia in orthodox views, but will be distinguished in lateral films Some degree of collapse may be detected within the lesion of primary atypical pneumonia, but gross collapse suggests the existence of some other condition. An appraisal of the interpretation of the radiological findings in atypical pneumonia appears below

Complications.—Primary atypical pneumonia is usually regarded as a benign condition which has few complications This appears probably to be the case, but as a careful follow-up of cases of the condition has yet to be made, it is not possible to state that there are no sequelæ There are two forms of complication recorded which are of interest, and also an important negative finding The fact is that primary atypical pneumonia rarely appears to lead to superadded pulmonary bacterial complications This circumstance, which may be contrasted with influenza, may be related to the pathology of the disease It seems probable that the existence of a destructive lesion of the bronchial epithelium, such as is found in influenza, is of importance in connection with the ability of bacteria to survive in and attack the lower respiratory tract. As will be mentioned again below, the bronchial epithelium probably remains intact during primary atypical pneumonia, and this may be the reason why bacterial pneumonia so seldom seems to supervene

The complication of hæmolytic anæmia has now been recorded several times in primary atypical pneumonia The patients thus affected usually had high or exceptionally high titres of cold agglutinins in their serum, and such seem to be responsible for the hæmolytic episodes, which may occur as the pneumonia is subsiding Splenomegaly apart altogether from hæmolytic anæmia is occasionally found during the acute stage of primary atypical pneumonia Its cause is unknown

Neurological manifestations have also been described (Holmes, 1947, Jennings, 1952) The clinical picture has included polyneuritis, lymphocytic meningitis, or even encephalitis There is no certain basis for the view that the illness in these patients was primary atypical pneumonia, as described above The essential phenomenon was the co-existence of a lesion of the respiratory tract categorised as an atypical pneumonia and neurological symptoms and signs Much the same neurological pictures may follow other conditions, and occur sporadically at other seasons of the year They have been described, for instance, after influenza epidemics

Their significance cannot be assessed in relation either to influenza or to primary atypical pneumonia at the present time.

Illustrative cases of primary atypical pneumonia

The following case reports are of two patients seen in Sheffield early in 1950. They appeared to form a part of two family outbreaks, and though not previously in contact, they were both admitted to hospital within a period of three weeks. Both suffered relatively severe attacks of the disease

CASE 24. *Primary atypical pneumonia*

Mrs. C. J., housewife, aged 29, admitted to hospital on 4th February 1950, having been treated at home for a week as a case of pneumonia. She

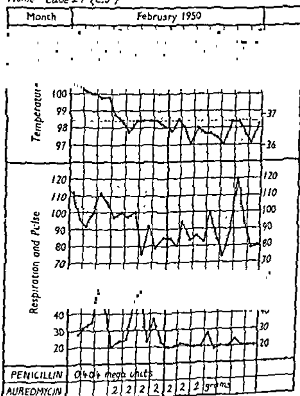


FIG 82

usually suffered from wheezing of the chest during common colds, but had never been ill before Two weeks before admission shivering and sweating began and cough with grey sputum developed There was some pain over the left costal margin a week before admission and also some malaise,

but no headache, sore throat or nasal symptoms. Shivering and sweating continued on and off.

Cough was frequent and irritating, and sputum green with occasional blood-tinge. In spite of the low degree of pyrexia (100 6° F.), tachycardia up to 110 was present, and the patient was unusually dyspnœic and cyanosed. There were bouts of tachypnœa up to 50 respirations a minute (Fig. 82). Signs in the chest consisted of impaired percussion at the right base, numerous râles over the right middle and lower lobes and a few râles at the left base. There was no bronchial breathing. X-ray showed extensive mottling in the right lower and mid zones, but there was also some mottling in the left lung (Fig. 83), and these changes persisted for ten days after admission, with slower resolution in the right than in the left lung. Sputum was mucopurulent and showed normal nasopharyngeal flora. Leucocyte count was 10,400 per cu. mm., with some shift to the left, and later 7,400 per cu mm The sedimentation rate was 47 mm (Wintrobe). The serum on the day of admission showed cold agglutinins in a titre of 1 in 1,200 using 0 2 per cent Group O cells, and five days later had increased to 1 in 2,000 and in a further eight days to 1 in 4,000. Serological investigations indicated that influenza virus A and B, *Rickettsia burneti* and the psittacosis virus were not concerned.

Treatment with penicillin for the first two days after admission was changed to aureomycin because of the general clinical picture and absence of improvement, but no immediate improvement was seen on a dosage of 2 grams daily for a week, and the patient did not begin to enter convalescence clinically until two weeks after admission The sedimentation rate did not fall until one month after admission The X-ray was normal five weeks after admission (Fig. 84) Of the patient's four family contacts, two had minor respiratory illness while the patient was in hospital, and one of these had a raised cold agglutinin titre of 1 : 128, two of the others being negative

Bronchogram carried out in August 1951 revealed a normal bronchial tree

CASE 25 *Primary atypical pneumonia*

Mrs M K, housewife, aged 28, admitted to hospital on 12th January 1950, having been treated by her doctor at home for a week as a case of pneumonia She had an attack of pneumonia in 1949, but had been well and in usual health until six days before admission, when she felt cold and unwell and shivered. There was some constricting pain over the left lower chest worse on coughing Cough was at first dry, but later sticky, pale green sputum without blood was raised with difficulty The temperature varied between 101 6° and 103° F., the pulse 120–140 (Fig. 85) She received treatment at home with sulphonamide tablets, but did not improve after these or after administration of penicillin at home Headache, anorexia and constipation were the only other symptoms noticed There was no sore throat or coryza, nor was the voice hoarse On admission there was a low, irregular fever, and the patient was dyspnœic, though the respirations were not raised above 30 and there were periods of tachycardia up to 136 The chest showed slightly diminished movement and diminished air-entry with only slight impairment of percussion over the right lower lobe There were a few râles but no bronchial breathing

polymorphonuclears, and five days later the total leucocytes numbered

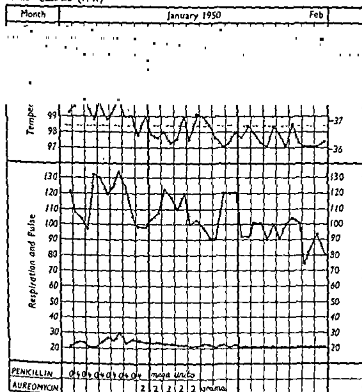


Fig. 85

11,600 *per cu. mm* The serum showed a cold agglutinin titre of 1 : 256 on admission and 1 : 10,000 five days later, rising to 1 : 20,000 eight days after this The sedimentation rate, which had to be performed at 37° C., was 8 mm The spleen was felt for the first time five days after admission. Treatment with penicillin for the first six days produced no clinical improvement, though the temperature fell Aureomycin in dosage of 500 mgm six-hourly given for four days produced immediate subjective improvement and a remarkable clearing of the X-ray shadows (Fig 87)

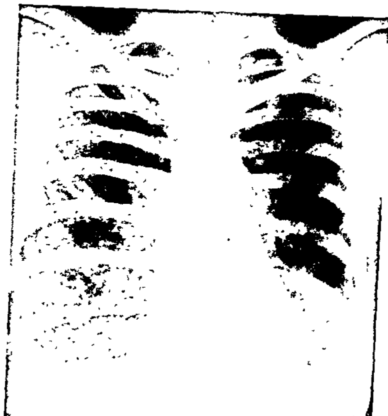


FIG 86—Case 25 M K Primary atypical pneumonia
Radiograph on the 12th day of illness, showing coarse miliary opacities throughout both lung fields

Sputum, if anything, increased, but was still raised with difficulty and was stringy and colourless Convalescence was, however, slow and the enlargement of the spleen persisted even after discharge. The cold agglutinin titre had begun to fall four weeks after admission, but was elevated above normal for a further four weeks. Serologically, no rise in antibodies occurred to either influenza virus A or B, and no antibodies [illegible]

one a titre of 1 128, the remainder being within the normal range of 1 . 32 or less using 0 2 per cent Group O cells.

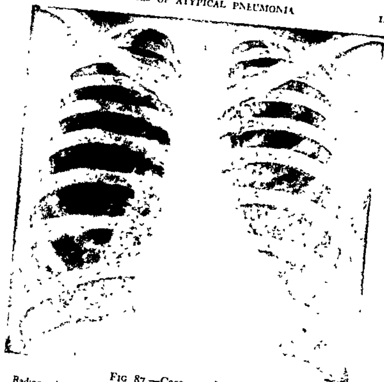


FIG 87 — Case 25 M. K

Radiograph on the 19th day of illness, showing clearing of both lung fields

Primary atypical pneumonia in a serviceman

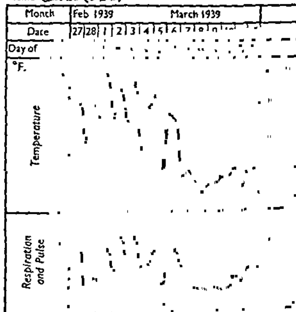
The following case report is also given because the illness formed part of an outbreak of febrile catarrh at a naval training establishment. Serological studies did not suggest that either of the influenza viruses A or B were concerned in this patient's illness

CASE 26 *Primary atypical pneumonia*

J E B, aged 18, became gradually ill on the 21st February 1939, with a cold, sore throat and a cough The nose was blocked There was no fever, and after a few days he improved On the 26th he began to shiver, developed a frontal headache and had renewed cough He was worse again on the 27th, and had pains in the back of the thighs Cough was dry and irritating The voice was normal He had had no previous respiratory tract illness When seen on the 28th the temperature was 102 F and pulse 80 (Fig 88) The face was flushed, with slightly cyanosed lips The eyes were glistening and the tongue coated The nose was obstructed, the pharynx injected and the tonsillar glands were slightly enlarged The

chest showed an area of fine râles at the left base with altered breath-sounds. A rhonchus was heard in the left axilla

Fever and cough continued, and yellowish, mucopurulent sputum was raised from the 1st March onwards On the 3rd there was slight hoarseness of the voice, râles were still heard at the left base, but the breath-sounds were normal. The sputum was streaked with blood X-ray on the 2nd March (Fig. 80) showed ...
the right ...
opacity ...
7th March ...



were heard over the upper as well as the lower zones On the 14th March the patient was feeling well and the cough was now dry X-ray on the 27th March ...
b ...

... ere not made, but the patient was clinically well at the time the last X-ray film was taken.

Interpretation of the radiological findings in atypical pneumonia

The findings in the patient J E B are of some interest because they illustrate the great difficulty which arises in the interpretation

of the X-ray appearances of atypical pneumonia. In the first place, the illness occurred during an outbreak of respiratory tract infection. Secondly, the patient had a severe illness with high swinging fever, constitutional symptoms, cough and sputum. He had never had any previous chest disease. Thirdly, though physical signs were

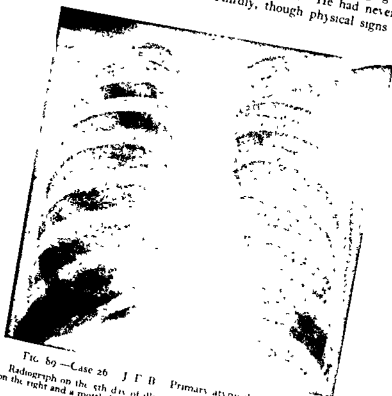


Fig. 69.—Case 26. J. F. B. Primary atypical pneumonia. Radiograph on the 5th day of illness, showing an enlarged hilar shadow on the right and a mottled opacity in the left mid zone.

confined to the left lung, where a mottled lesion was seen radiologically, there were radiological abnormalities on the right side as well. The interpretation of the right sided lesion is clearly impossible without lateral films, but as the hilar shadow extended it appeared to become associated with a collapse, probably of the middle lobe. Yet the whole clinical picture argued strongly against any simple mechanical condition such as might be the cause of a collapsed lobe.

FIG 90 —Case 26 J E B

FIG 91 —Case 26 J E B

The following patient, Miss B N, illustrates a case of pulmonary collapse occurring during a minor respiratory illness

CASE 27. *Pulmonary collapse of unknown origin*

Miss B. N, aged 24, developed a cold and slight cough on 1st October 1951. She had slight malaise, but cough had persisted, and after



FIG 92 —Case 27 B N Pulmonary collapse of unknown origin

Fig 92 —Radiograph on the 9th day of illness showing a triangular shadow at the right base Lateral X-ray suggested an interlobar effusion The right lower lobe was normally expanded

a violent attack of coughing there was a little blood-streaked sputum on the 9th October Her previous chest X-rays had always been quite normal but on the 9th October (Fig 92) there was a shadow extending from the

Fig 90 —Radiograph on the 10th day of illness 2 days after Fig [illegible] showing similar appearances The hilar shadow on the right side has extended towards the periphery

Fig 91 —Radiograph 6 weeks after admission The left lung has cleared The right lung shows a collapse probably of the right middle lobe The right upper zone is now mottled

FIG. 93 —Case 27 B. N.

FIG 94 —Case 27 B N

right hilum downwards in the paravertebral position This shadow was sharply outlined; there were no other opacities in the lung fields A lateral view showed only a shadow resembling an interlobar effusion in the oblique fissure; the lower lobe was normal. But a view in the hyper-lordotic position (Fig. 93) showed that the shadow was due to a collapsed right middle lobe. The patient remained afebrile, cough speedily diminished and X-ray on the 24th November (Fig 94) showed that re-expansion of the collapsed lobe had occurred

Now, there was no illness in this patient comparable with that in the cases of primary atypical pneumonia already described The diagnosis of atypical pneumonia was never suggested, and yet radiological abnormalities appeared during the course of a minor respiratory illness. Some authorities might have diagnosed the case as one of primary atypical pneumonia Others would have considered that the condition was due probably to mechanical blockage of a bronchus by mucus, and was not a pulmonary infection at all

Minor radiological changes accompanying colds, catarrhs and other respiratory tract infections were described by Ramsay and Scadding in 1939 They were encountered among patients seen at a tuberculosis clinic and in whom trivial respiratory catarrhal symptoms had occurred The lung lesions were thought to result from an aspiration of mucus from the upper respiratory tract which had led to an atelectasis of a broncho-pulmonary segment Inflammation in the atelectatic lobe or segment occurred subsequently, and the condition was then termed an 'aspiration pneumonia' Scadding (1948) points out that such aspiration pneumonias occur particularly in patients with chronic bronchitis, asthma or other chronic disease of the upper respiratory tract Recently, Wrath (1951), working at an R A F mass miniature radiography unit, has reported similar transient X-ray shadows in the chest in 1.8 per 1,000 of 38,346 persons The affected individuals were all young male adults, many of whom had recently returned from abroad They had minor symptoms, such as a cold, or cough or sputum, or aching in the chest. Only two were febrile The radiographic changes were opacities in a broncho-pulmonary segment or occasionally in a whole lobe with evidence of partial collapse The condition was again regarded as a result of aspiration of material into the lungs Robertson and Morle (1951) have also described a large series of

Fig 93.—Radiograph in the hyper-lordotic position showing collapse of the right middle lobe

Fig 94.—Radiograph 6 weeks later showing normal appearances

cases in servicemen with radiological abnormalities in the chest during outbreaks of upper respiratory infection. The subjects suffered from illnesses with fever, cough and sputum, and resembled cases of atypical pneumonia, in that the chest showed radiological opacities confined to broncho-pulmonary segments in one or more lobes, usually in the lower lobes. Robertson and Morle considered that the anatomical localisation of the lesions in dependent segments indicate that an aspiration of products had occurred from an associated upper respiratory infection, and that the condition was unlike a virus infection. Yet they classified their patients as suffering from primary atypical pneumonia.

It will thus be apparent that considerable controversy exists concerning the interpretation of the radiological lesions of primary atypical pneumonia, and thus of the syndrome itself. This is probably because so little is known concerning the underlying pathology or of the pathology of the minor radiological abnormalities of the lung. Thus, there is no reason to think that all the various radiological changes described in association with the minor respiratory illnesses are necessarily of the same pathology or ætiology as are those associated with the syndrome of primary atypical pneumonia. The fact that radiological changes analogous to those seen in the latter condition are found in cases of psittacosis and of Q fever is evidence that they can at times be produced by infective processes initiated by virus or rickettsial agents.

Pathology and diagnosis of primary atypical pneumonia

As the condition is rarely fatal, few observations other than radiological ones have been made concerning the actual lung lesion in primary atypical pneumonia. Parker, Jolliffe and Finland, however, described in 1947 the autopsy findings in eight fatal cases The lungs showed scattered non-crepitant areas, and on the cut surface remarkable greyish miliary nodules, chiefly in the lower lobes The lesions comprised an alveolar exudate of mononuclear cells and an infiltration with plasma cells in and around the walls of bronchioles and blood-vessels An intact bronchiolar epithelium existed even in cases with polymorph cells within the lumen, and this feature presented a striking contrast to the findings in fatal cases of influenza already described.

In life, the serological changes found in the group of cases of atypical pneumonia of unknown ætiology are those already referred to as the appearance of cold agglutinins and, in addition, agglutinins

also appear in some cases for the M.G species of non-hæmolytic streptococcus of Thomas and others (1945). Cold agglutinins for human red cells demonstrable at 4° C but not at 37° C. are found in a variety of diseases, such as glandular fever, malaria and hæmolytic anæmia. They are therefore not specific for any one condition. All observers are, however, agreed that the actual concentration of the agglutinins in the sera from cases of primary atypical pneumonia is higher on the average than that found in other conditions, and that the titre rises as the patient enters convalescence (Finland and others, 1945; Finland and Barnes, 1951). Nevertheless, the test is affected by many circumstances, including the individual donor's red cells, the concentration of the cells, the manner of removal of serum from the clot, storage and so on. No standardised test exists which enables the significance of a particular titre to be assessed. But whatever the concentration of red cells used, a titre such that the serum will still produce agglutination if diluted two hundred times or more is in excess of that encountered in the normal. Such a titre would be suggestive of primary atypical pneumonia, and if the titre had risen to this height from a level of 1 : 50 or less as the disease progressed, the likelihood that this was the diagnosis would be greater. It must not be forgotten, though, that similar high titres may be found in other diseases, and even in occasional cases of staphylococcal or pneumococcal pneumonia. It is desirable that sera from normal controls should always be included in tests for the determination of the titre of cold agglutinins in patients, as a check on the sensitivity of the particular technique.

The agglutination of the non-hæmolytic streptococcus (strain M.G.) is also found with convalescent serum rather than with serum from the acute stage of illness. The titres are never very high. There is no strict correlation with the presence or absence of cold agglutinins. At present there is no reasoned explanation of the development of streptococcal or of cold agglutinins in cases of primary atypical pneumonia.

The blood shows no characteristic leucocyte changes in primary atypical pneumonia, there being neither leucopenia nor leucocytosis.

It will be clear that the differential diagnosis of primary atypical pneumonia is one of exclusion first of known causes of the syndrome of atypical pneumonia, such as psittacosis and Q fever. The lack of antibodies to the agents of these conditions in the early convalescent serum is, however, too late a finding to be of help in the acute stage of illness. A high titre of cold agglutinins or of streptococcal agglutinins may be found in the serum by the end of the first week,

and becomes of greater significance if enhanced in a later specimen The combined clinical, radiological and laboratory data serve to build up a positive diagnosis of primary atypical pneumonia. Lack of response to penicillin is important. Response to treatment with antibiotics such as aureomycin, chloramphenicol or terramycin is not, however, of value in differential diagnosis because some patients show this effect and others do not (see Chapter 14)

Ætiology of primary atypical pneumonia

The earlier observations on the sputum and nasopharyngeal secretions of cases of primary atypical pneumonia suggested that the condition could be transmitted to a variety of laboratory animals Control studies with material from healthy individuals or autoclaved specimens soon showed that the lung lesions observed in the animals could be traced to an inapparent animal infection which had been latent prior to the inoculation. Latent viruses capable of producing pneumonia after activation have been found in mice (in whom several different virus agents are now known to be capable of producing latent infection of the lung), in hamsters, cotton-rats and pigs Some of these animal agents appear to be related to the psittacosis-ornithosis group of viruses; others are unrelated But, in general, the agents are only capable of producing pathological effects in the lungs of the animal species in which they occur in nature. Cultivation in fertile hens' eggs often fails with such viruses The agents are also pneumotropic, and produce no lesions outside the respiratory tract They must be inoculated intranasally under an anæsthetic if a lung lesion is to be produced.

In 1944, Eaton and others described the recovery of a virus capable of producing lung lesions when inoculated intranasally under an anæsthetic into cotton-rats. This virus was cultivated from the sputum of a case of primary atypical pneumonia by amniotic inoculation into hens' eggs The lungs of the infected chick embryos were infective for the cotton-rat, and produced in a proportion of animals purplish areas of consolidation at the hilum or spread throughout the lung, and looking macroscopically like the lesions of influenza virus in mice or ferrets Eaton attempted to guard against the latent infection of the cotton-rats by their own pneumotropic virus by vaccinating them with a strain of the latter agent before use. He also maintained the virus obtained from sputum by passage only in eggs. Control studies with sterile egg material did not produce lung lesions in the cotton-rats of the same character and frequency as did the infected chick embryo lungs Hamsters were as susceptible as

cotton-rats to the chick embryo material In the writer's hands, Eaton's virus produces lung lesions more readily in hamsters than in cotton-rats The essential lesion in the hamster is an area of cellular infiltration much more solid in character than influenza virus infection in mice or ferrets The bronchiolar epithelium is intact, but there may be an exudate in the lumen Peri-bronchial and perivascular infiltration with round cells is constant (Figs 95–98). Though the lungs may be severely affected, there are few signs of illness, and death is exceptional Infected chick embryos are somewhat retarded in growth, but appear otherwise normal Eaton has succeeded (1945) in developing a neutralization test with chick embryo virus inoculated into cotton-rats and hamsters He found that neutralizing antibodies were present in the sera of human cases of primary atypical pneumonia during convalescence, but not in the acute stage. As, however, other workers have demonstrated antibodies to normal and infected animal tissues in the convalescent sera from cases of primary atypical pneumonia, Eaton's serological results are not completely convincing The situation is that Eaton's virus is the only pneumotropic agent capable of cultivation in the chick embryo lung which has any claim to having been recovered from a human case of primary atypical pneumonia rather than an animal source. It produces lesions which are analogous to the human lesions of primary atypical pneumonia in those few fatal cases which have occurred and which have been investigated histologically (see above) But no other observer has been able to repeat Eaton's observations by recovering another strain of virus with similar characters to the original agent, and many such attempts have been made

The Commission on Acute Respiratory Diseases carried out an exhaustive series of bacteriological observations on cases of atypical pneumonia, and failed to demonstrate any significant abnormality in the nasopharyngeal flora (1944*b*) They then carried out observations (1946) on human volunteers similar to those described in connection with febrile catarrh (Chapter 7) These results indicated that human volunteers inoculated by breathing a spray of atomised droplets of sputum and throat-washings from cases of primary atypical pneumonia developed a clinical and radiological syndrome analogous to that of the original cases in about 25 per cent of instances Minor respiratory illness without radiological changes developed in other volunteers The incubation period of the atypical pneumonia was seven to fourteen days, depending on whether the material was filtered or unfiltered Filtrates had the longer incubation … d

autoclaved material rarely produced cases of atypical pneumonia and only occasional instances of minor illness. Isolation of the volunteers was extremely rigid, and on one occasion when autoclaved material gave apparently successful transmission of disease it was

FIG 95–98.—Histology of pneumonia due to the virus of Eaton in cotton-rats and hamsters



FIG 95

FIG 95.—Consolidated area of lung in cotton-rat 7 days a[illegible] with chick-embryo lung containing Eaton's virus (L.P.) The alveoli and interstitial tissues are infiltrated with mononuclear cells Perivascular infiltration surrounds the vessels The bronchioles were normal in this lung

FIG 96.—Consolidated hamster lung 7 days after infection with chick embryo culture of Eaton's virus (L.P.) The bronchioles and vessels are infiltrated with plasma cells and round cells An exudate fills the bronchioles. The alveoli are infiltrated with mononuclear cells

found that isolation of the infected persons had broken down A repetition of the experiments with rigid isolation gave negative results with autoclaved material Inoculation of volunteers who had previously been inoculated with material from cases of febrile catarrh (A R D) did not reveal any cross-immunity to primary atypical

atypical pneumonia are the influenza viruses. In fact, although sporadic cases of primary atypical pneumonia have been recorded during influenza outbreaks, it is exceptional to encounter this syndrome in association with influenza virus infection. When it does occur, the possibility always exists of simultaneous infection with more than one virus agent, so that there is no proof that the lung lesions are induced by the influenza virus.

There is no theory available concerning the ecology of the hypothetical virus of primary atypical pneumonia which gives any clue to its mode of survival and transmission. Analogy with the pneumotropic viruses of animals would perhaps suggest that if a human pneumotropic virus exists, then it is more likely to be present in a quiescent or latent condition unassociated with any pathological lesions than the converse. The reason for its association with such lesions might be explained by some circumstances affecting the lower respiratory tract, such as an increased accumulation of secretion, or perhaps an increased blood-flow. The pathology of herpes labialis in man suggests that the herpes virus is quiescent for most of its life within its host. If the latter experiences what Andrewes has described as a 'jolt', and which may in the case of herpes be a cold, or an attack of pneumonia, or an injection of some foreign material, the host-virus balance is upset and lesions appear. It seems possible to the author that some such 'jolt' may convert a latent pneumotropic virus into one productive of pathological lesions. This would explain the increased incidence of primary atypical pneumonia during outbreaks of febrile catarrh—a disease due almost certainly to a different virus.

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CHAPTER 9

PSITTACOSIS AND ORNITHOSIS

THE existence of a relatively severe disease of the respiratory tract with pneumonia, and traced to contact with infected parrots or budgerigars, has long been known (Ritter, 1880). Extensive outbreaks occurred in several countries in 1930 The virus of psittacosis was first recovered in Britain by Bedson and others (1930), and independently in Germany by Levinthal (1930) and in the U.S.A. by Krumwiede and others (1930) The infection produced by this virus was at first regarded as a severe and often fatal complaint, but milder illnesses due to the same agent were later recorded and similarly traced to contact with sick parrots or budgerigars. The recovery of similar viruses (ornithosis) from fulmar petrels, pigeons, domestic fowls and chicks from 1938 onwards led to a realisation that psittacosis is only one of a range of virus agents pathogenic for man but usually associated with birds. Human infection derived from infected petrels, pigeons and so on was also recorded in the form of sporadic cases or in small outbreaks, though it was realised that such infection was frequently accidental, and by no means as frequent as would be anticipated from the widespread natural occurrence of the viruses

The description of cases of atypical pneumonia from the middle 1930's onwards led at first to the expectation that viruses of the psittacosis-ornithosis group would be found to be ætiologically concerned A few such cases either occurring sporadically or in outbreaks were, in fact, found to harbour viruses such as the meningopneumonitis agent of Francis and Magill (1938) or the S.F. virus of Eaton, Beck, and Pearson (1941) and these agents are now known to belong to the same group of viruses as those derived from birds. The majority of cases of primary atypical pneumonia in man yielded no such agents, but in a minority (10 per cent) serological changes occurred which suggested infection by an agent related to psittacosis. These cases were milder in type than psittacosis, and their exact relationship to the psittacosis group of virus infections is unknown

The viruses thus concerned in the psittacosis-ornithosis group possess similar biological characters and antigenic components. They are larger in size than the influenza viruses, and may be

stained and demonstrated in microscopical preparations (elementary bodies).

Clinical features

Just as in the case of other infections, psittacosis in man constitutes a variable condition with a severe typhoid-like illness at one end of the scale and a mild illness resembling influenza at the other. It seems probable that the lung is involved in the majority of instances, and extensive consolidation is invariably found in fatal cases. Milder cases vary, and though physical signs may be found in the chest, radiological examination is not always confirmatory of the existence of pneumonia. The following description is based on a moderately severe attack of psittacosis.

After an incubation period of seven to fourteen days, there is a sudden onset with pyrexia, headache, shivering, malaise, pains in the limbs and back. There may be epistaxis and photophobia, vomiting or diarrhœa may occur in the early stages, but alimentary symptoms are usually trivial. The fever is usually continued or remittent, the pulse is relatively slow, but may rise as the disease progresses. Towards the end of the first week, when the temperature is still climbing, the initial dry cough may become slightly productive and signs in the chest may be elicited. These signs consist of areas of weak breath-sounds or bronchial breathing and of râles, and they coincide radiologically with patchy areas of consolidation in one or both lungs. Dullness is slight at first, but may become more evident as the disease progresses. The pleura usually escapes involvement. In spite of extensive consolidation, and though the respiration rate is raised, the degree of dyspnœa may be slight. The general picture does not suggest a frank pneumonic consolidation, and sputum is rarely abundant, being mucopurulent, and blood-streaked only on occasions.

In severe illnesses a typhoid-state may be present with drowsiness and prostration, or a low muttering delirium. The spleen is occasionally palpable, and scanty rose-spots were described by Horder and Gow (1930), but these are not found at all commonly. The temperature begins to fall about the seventh or eighth day in mild cases, but remains elevated in the second week in more severe illnesses. It then decreases by lysis. A rising pulse-rate, coma, deepening cyanosis and a low blood-pressure are unfavourable signs. Complications include thrombo-phlebitis, but are rare. Nervous system signs described by Thomson and Hillier (1930) included an impassive facies suggestive of Parkinsonism, exaggerated reflexes,

pupil changes and weakness of the cranial nerves. The leucocy count is normal, or a leucopenia may be present. Convalescence slow in severe cases, and relapses may occur.

Death is more likely in elderly subjects, and the disease i apparently mild in those under 20 years of age. It seems probabl that many mild illnesses escape attention unless contact with sic birds suggests the possibility of infection from this source. Thu among a group of five cases among keepers at the London Zo recorded in 1939 (Troup and co-authors, 1939), two patient developed attacks of pneumonia and one died, two suffered attacks diagnosed as influenza, and the fifth experienced an illness accompanied by cough and sputum with abnormal signs in the chest. A wider use of radiology in minor illnesses would probably result in the frequent detection of changes in the lungs which were unsuspected clinically.

The six cases described by Eaton, Beck and Pearson (1941) from whom a psittacosis-like virus termed the S.F. meningopneumonitis strain was isolated were all severe illnesses. The initial patient, who had not been in contact with parrots or other psittacine birds, died with a broncho-pneumonia. Three nurses who nursed the patient were taken ill and two died. Two laboratory assistants working in the laboratory where the virus from the earlier patient was under study constituted the fifth and sixth cases, which were milder. Other instances of patient–nurse contagion have been recorded in infections with the psittacosis–ornithosis group of viruses, and such contact-infections appear often to be severe or fatal.

Pathology and diagnosis

The morbid anatomy of fatal cases of psittacosis is that of a consolidation of the lungs, of focal necrosis of the liver, and enlargement of the spleen. Hæmorrhages may be found in organs such as the adrenals and muscles, and the brain and cord may be congested and œdematous. The histological character of the lung lesions is that of a confluent broncho-pneumonia with mononuclear cell infiltration of the alveolar walls and formation of an alveolar exudate composed of mononuclear and polymorphonuclear cells. The overall picture, however, suggests that infection by the virus is generalised, and this is known to be so because virus can be recovered from the blood during the first week of illness.

Diagnosis can only be made certain by a demonstration of the virus concerned or by serological means. Virus can be recovered by

inoculating mice intraperitoneally with citrated or defibrinated blood or with sputum. Alternatively, eggs may be used. These are inoculated with material in which sulphonamide and streptomycin are incorporated in order to restrain bacterial growth. The serological test usually employed is that of complement-fixation with an antigen prepared from infected mice or eggs. The reader is advised to consult a reference book such as *Diagnostic Procedures* (1948) listed below for full details. As in other serological tests, two specimens of serum should be examined, one taken in the acute stage of illness and the other during convalescence. A rising titre of antibodies (four-fold or more) is evidence that the recent illness was related to infection by one of the group of viruses concerned. Sera from patients with lymphogranuloma inguinale may give positive results because of cross-reactions between psittacosis and the virus of lymphogranuloma.

The leucocyte count is not of great value in diagnosis, though a leucocytosis does not occur. Serological changes which occur in primary atypical pneumonia, such as cold agglutinins or agglutinins to the streptococcus M G species, do not develop in psittacosis.

Epidemiology

In all the infections of this group the virus is believed to be derived from infected birds. Psittacosis in parrots is often symptomless, the virus being excreted in large amounts in the droppings. However, in many human outbreaks the original infected birds were obviously sick, with ruffled feathers, and some died. In pigeon aviaries where ornithosis infection is endemic the adult birds may appear healthy, but a high mortality may occur amongst the young.

Human infection appears to occur by inhalation of dust containing infected droppings, or from bites, or by handling or stripping infected birds. Case-to-case transfer of infection has occurred in nurses or doctors in contact with patients, as already mentioned. It seems probable that some viruses in the general psittacosis–ornithosis group are less infective for human beings than are others. Andrewes and Mills (1943) demonstrated a psittacosis virus from apparently normal pigeons in England. Yet illnesses resembling atypical pneumonia have not been recorded to any extent in pigeon-fanciers in this country, though they have been described in America (Meyer, 1942). The outbreaks in the Faroe Islanders derived from handling fulmar petrels are, by contrast, evidence of a relatively high pathogenicity for man.

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CHAPTER 10

Q FEVER

It would have seemed ridiculous to have included a chapter on Q fever if this book had been written even as little as seven years ago. Yet it is now known that infection with *Rickettsia burneti*, the causal organism of Q fever, is not uncommon in certain parts of Britain and that it occurs in many parts of Europe, North Africa, the U.S.A., Australia and elsewhere. All this has happened since 1935, when the fever was first described by Derrick among meat- and cattle-workers in Queensland, Australia, and was shown to be caused by a rickettsial agent by Burnet and Freeman (1937). The epidemiological associations observed in the field led Derrick (1944) to suggest that cattle were infected from a wild animal reservoir, such as the bandicoot, by means of ticks infesting both animal hosts. Men were thought to be infected by inhaling infected cattle-tick fæces, but this conception, though theoretically possible, has been succeeded by other views.

Rickettsia burneti was next recovered from ticks caught in Montana and found to be harbouring a hitherto unknown organism (Davis and Cox, 1938). The human pathogenicity of the rickettsiæ was shown by the occurrence of outbreaks of infection among the laboratory staff working in Institutes where the organism was being studied. No more was heard of the disease until the war years, when the outbreaks of primary atypical pneumonia among troops in the U.S.A. and elsewhere led to intensive studies of possible ætiological agents. The Mediterranean armies fighting in Italy began to suffer from explosive outbreaks of febrile disease early in 1944. Radiological examination of the chest revealed the frequent existence of pneumonic changes, and the condition was classified as atypical pneumonia. But Robbins and co-authors (1946) working in an American field laboratory at Naples recovered *R. burneti* from the blood of patients with the disease, and serological studies showed the infection to be widespread among the troops and in servicemen recently returned from the war theatre in Italy. The inference from these studies was clearly that Q fever could present as an infection of the respiratory tract mimicking either influenza or atypical pneumonia in individuals without any obvious contact with an animal host. Since the end of the war, Q fever has been found

among meat-packers at factories in the U.S.A., among dairy-farmers in California, and in Germany, Switzerland, Greece, Turkey and Morocco. In Great Britain a small outbreak of Q fever occurred among the staff at the Royal Cancer Hospital, and this was traced to a source of infection from dairy-herds in Kent (Marmion and Stoker, 1950). A recent outbreak occurred at an art school in Canterbury, and it is possible that the unwrapping of a statue packed in straw was the initiating focus of this outbreak (Harvey and co-authors, 1951) Straw has been thought to be the cause of outbreaks elsewhere, and as the rickettsiæ concerned in Q fever are unusually stable, survive desiccation and persist in dust, this hypothesis is quite a reasonable one.

Studies have recently been made by Stoker and others (1952) on sera from blood-donors collected in various parts of Britain Kent and Devon, Gloucestershire, Wiltshire, Derbyshire, North Wales and Oxfordshire have all yielded evidence of the existence of Q fever in man either because of recent cases or by the detection of antibodies in sera As antibodies persist for a long period after infection, this can only mean that *Rickettsia burneti* is, and has been for some time, a cause of endemic and possibly of epidemic disease in Britain. The mode of spread of infection will be considered below, but cattle seem to represent the usual animal reservoir from which the human disease is derived This is not necessarily so in all parts of the world. For instance, in North California (Lennette and Clark, 1951) sheep and goats are apparently more heavily infected than the cattle, whereas dairy-cattle furnish the reservoir in South California (Huebner and Bell, 1951).

Clinical features

Most observers agree that Q fever is an acute febrile disease with symptoms in the early stages suggestive of influenza The average duration of fever is, however, longer than in influenza, and as the illness progresses the picture is essentially that of a pyrexia without any obvious localising symptoms or signs It is particularly necessary to stress that, with the exception of cough and chest pain, symptoms or signs referable to the respiratory tract are not prominent. The signs in the chest are also indefinite, and though radiological changes are frequently found, the cases do not resemble ordinary bacterial pneumonia from the clinical point of view.

The detailed symptomatology may be seen by reference to Table 18, compiled from the reports of various workers. The cases reported by Denlinger (1949) from South California and by Feinstein

and co-authors (1946) from an outbreak at an American Air Force station in men returning from Italy were in patients admitted to hospital The larger series from North California by Clark and others (1951) was in patients under the care of individual practitioners.

TABLE 18

Q Fever

Percentage Frequency of Symptoms and Signs

Symptoms and signs	Q fever in California		Q fever from Italy 1945 (Feinstein and others 1946) 128 hospital cases
	S. California, 1947–49 (Denlinger, 1949) 80 hospital cases	N. California 1948–49 (Clark and others, 1951) 180 patients	
Sudden onset	92.5	72	—
Fever	100	100	70.5
Chilliness or rigors	83.7	74	75.4
Malaise	93.7	100	40.6
Headache	Very common	65	50
Backache	12.5	47 (muscle pain)	75
Anorexia	53.6	43	24.2
Nausea	32.5	22	36 [illegible]
Vomiting	26.2	13	15.6
Cough	62.5	24	62 [illegible]
Chest pain	36.2	10	35 [illegible]
Sore throat	2.5	5	24.2
Coryza	3.6	4	23.4
Chest signs	58.7	21	55.5
Râles	26.2	3	32.8
Dullness			
X-ray changes	84.4 (77 patients)	34 (65 patients)	100

After an incubation period of fourteen days to a month, the illness begins abruptly with headache, muscular aching, chilliness or actual rigors and anorexia The patient is usually moderately ill, complaining chiefly of headache, and exhibiting a fever of a remarkably remittent or intermittent character with frequent sweating The pulse rate is relatively slow, and apart perhaps from a dry cough or a few râles in the chest, there are no abnormal signs Cough, however, may become more prominent towards the end of the first week, though still dry. In one-third of patients it is accompanied by chest pain of a pleuritic character The throat may show some injection of the pharynx without exudate, but sore throat and nasal symptoms are minimal Some degree of neck stiffness is occasionally found. Neither the liver or spleen may occasionally be palpable, or else the

hypochondrium is tender to palpation. Doubtful 'rose-spots' have been noted on the abdomen infrequently.

The duration of the fever and of the disease as a whole is extremely variable. The American airmen were febrile for from two to eight days after admission to hospital, but in California the duration was from two days to as long as three months, with an average of ten to sixteen days The severity of illness is equally variable, and many patients have exhibited an extremely mild illness. Nevertheless, the incidence of radiological changes is reported to be high among patients admitted to hospital. In such, localised areas of râles with altered breath-sounds and slight change in percussion resonance may be elicited in the area presenting abnormality by X-ray The opacities, which are usually single, are frequently segmental, but occasionally lobar. They may be dense and uniform in character, or hazy and of a 'ground-glass' structure. They occur chiefly in the middle or lower zones. There is an absence of hilar enlargement. The changes are occasionally accompanied by a small collection of pleural fluid Opinions vary as to whether the opacities are similar to those found in primary atypical pneumonia or not. However, in the cases which occurred in British troops in Italy the denseness of the opacities and their relatively sharp delineation suggested a bacterial pneumonia; Jacobson, Denlinger and Carter (1949), from Los Angeles, similarly consider that the shadows cannot be distinguished from pneumococcal pneumonia

The frequency of abnormal radiological changes is reduced by the inclusion of mild illnesses in the sample under study, and it is known that a proportion of cases of Q fever have no demonstrable radiological abnormality If found, lung opacities usually begin to resolve when the fever is over, but occasionally resolution is protracted and may require several weeks for completion.

In the series of 180 patients in North California described by Clark and others (1951), there were 30 patients whose fever lasted for more than a month Such protracted severe illnesses differed little from the shorter illnesses in symptomatology. Hepatomegaly was observed in some, however, and evidence of hepatic dysfunction developed in 4 patients Even after the fever was over, patients in the older age-groups remained weak, easily tired and depressed for long periods, and it is clear that Q fever may be quite a severe complaint.

Pathology and diagnosis

Q fever is rarely fatal, so that there is little opportunity for an examination of the pathology of the disease in the average type of

case. A fatal case in a laboratory worker was described in 1941, however (Lillie and co-authors, 1941), and recently Whittick (1950) described the morbid changes found in the patient responsible for the outbreak in the staff of the Royal Cancer Hospital. The lung attracted attention because of its general resemblance to lobar pneumonia. However, the histological picture was of a mononuclear exudate, with macrophages, lymphocytes and plasma cells which filled the alveoli and bronchioles. Whittick demonstrated rickettsiæ in abundance in the lung, in the brain, which showed foci of softening, and in the spleen, which was slightly enlarged.

In general, Q fever resembles other rickettsial infections in that the disease is a systemic infection involving the blood-stream, but it differs in that the predominant organ which is affected is the lung. This may be due to the mode of infection, which is air-borne via the respiratory tract, whereas the percutaneous route is the normal route of entry of the rickettsiæ of the typhus fevers.

The rickettsia of Q fever was at one time named *R. diaporica* because of its small size and ready passage through bacterial filters. It is more usually known as *R. burneti*, or by some American authors as *Coxiella burneti*. Its cultivation from the human patient can be effected by inoculating blood intraperitoneally into guinea-pigs or mice, or into the yolk-sac of fertile hens' eggs. A febrile disease develops in guinea-pigs thus infected, and sub-inoculation to mice intraperitoneally may enable a demonstration of the causative rickettsiæ in smears taken from the spleen and stained by Giemsa or the Macchiavello method. A more convenient method of diagnosis is that of the demonstration of antibodies to *R. burneti* in the convalescent serum from patients. Two tests are commonly employed—the agglutination test with a suspension of rickettsiæ prepared from infected mice or eggs and a complement-fixation test with similar antigens. In either case a positive result can only be interpreted as indicating recent infection if a specimen of serum in the acute phase gives either negative results or else a much lower titre of antibody than that found in the convalescent stage. This precaution is needed because antibodies persist in the serum for a considerable time after infection, so that a single positive result in the complement-fixation test may not reveal the time at which infection occurred.

Thus, as in the case of psittacosis, diagnosis must usually be based on laboratory tests. There is no diagnostic change in the blood-count, though the polymorphonuclear count is usually depressed in the early days of illness and rises later. The cerebrospinal fluid

usually normal, even in patients exhibiting meningism. (An account of the characters of strains of *R. burneti* recovered in Britain is given by Stoker, 1950.)

Epidemiology

There are so many possible sources of infection of man from infected animals that it is clear that no one source is likely to be responsible in every case. Many human outbreaks have occurred in those engaged in the care of dairy-herds, or in the slaughter-house, or in meat factories. Dust from infected hides or bones can readily lead to infection in man by inhalation, and it does not seem necessary to invoke the aid of ticks, though these have been shown to harbour Q fever rickettsiæ. It is difficult to believe that insect or anthropod hosts were not at some time in the past concerned in the ecology of *R. burneti*, but the accidental infection of man is clearly unimportant compared with its normal almost saprophytic existence in other mammalian hosts.

The disease in cattle is usually inapparent, and rickettsiæ are excreted in the milk, urine and dung, and are found in particularly heavy concentration in the placentæ from parturient cows. Infection by the ingestion of raw milk, or even from pasteurised milk, which may still contain viable rickettsiæ, is also theoretically possible, and may be responsible in those individuals who have not come into contact directly with the immediate environment of cattle. In some areas, sheep and goats rather than cows are believed to be the animal reservoir of the rickettsiæ.

The most baffling outbreaks of Q fever are those which have occurred explosively, this suggesting a simultaneous infection of a group of persons. Infected straw or hay harbouring dust from cattle-dung may be responsible in some such outbreaks. Occasionally dust from wool handled in a wool-carding plant or of bones in a glue-works may similarly be responsible. The clothes of a person handling cattle excreta or placentæ could similarly become a source of infection of other humans, and it is probably by such indirect means that the disease spreads to human groups. Direct contagion from man to man does not seem to occur at all commonly, except, for instance, in a post-mortem room, when a number of individuals may acquire an infecting dose of viable rickettsiæ.

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CHAPTER II

THE COMMON COLD

IT seems almost superfluous to attempt a definition of the common cold So persistent and ubiquitous is this affliction that there are few differences of opinion concerning the clinical phenomena of the cold. Nevertheless, the border-line between the minor respiratory illnesses seen during epidemics of influenza or of febrile catarrh and the common cold may be impossible to define, nor is it possible yet to identify the various clinical manifestations of the infection produced by the virus of the common cold itself, for progress in regard to knowledge of this agent is painfully slow. For the present, therefore, it is desirable to define a cold as an acute infection involving principally the nasopharyngeal region, usually afebrile or accompanied by a trifling degree of fever and constitutional upset.

Epidemiology

Maximum prevalence of colds is experienced in the autumn and winter, but apart from the first waves of infection in September and October, there are probably few periods in which incidence in the community could strictly be regarded as epidemic. There is indeed a continued endemicity punctuated by school outbreaks near the beginning of term and by family outbreaks throughout the winter. The summer season brings some relief from prevalence, however, [illegible] but [illegible] If s[illegible] a number of people embark on a ship [illegible] instance, when a number of people embark on a ship for a long [illegible] then the colds tend to die out until contact is made once again with another population Similarly, communities which owing to the weather become cut off from the rest of the world experience freedom from colds during these periods. Paul and Freese (1933) found that the people of Spitzbergen are largely free from colds during the winter, when they are isolated from the rest of the world, even though this is the period of minimum temperature. Within a few days of the arrival of the first ship in the spring, even if the people on board are in normal health, colds break out and spread rapidly through the population on land. Arctic explorers are also free from colds in polar regions, yet may develop them if clothes or blankets stored for months are opened, or as soon as they return home

Such experiences would suggest that normally constituted communities living in towns are being continually reinfected from without, and thus never attain the freedom from colds enjoyed by people living in isolation. Experience in schools in Great Britain has been recorded by the School Epidemics Committee of the Medical Research Council (1938) and by Cheeseman (1950) Peak incidence appears in the first four weeks of the term, though there may be a second peak towards the end of term In schools also there is a curiously higher attack-rate in girls (11–30 per cent in various terms) compared with boys (3–8 per cent) As this sex difference is not present during epidemics of influenza, it seems probable that it is a true phenomenon in relation to the common cold Nevertheless, until the common cold virus can be detected, as can the influenza virus, statistical records should be accepted with caution There is, in fact, considerable ignorance regarding the amount of morbidity due to colds in the general population. Some individuals suffer four or more attacks per year, others suffer only once or twice Age appears to bring a slackening in the number of attacks, but in those over 40 the lower respiratory tract becomes more frequently subject to what is normally termed 'bronchitis', and no one can deny the possibility that such may be in some way related to the cold virus It is indeed remarkable that so little is known about the epidemiology and experience of the commonest infection to which man is subject But the probability exists that acute sinusitis, otitis media, bronchitis and even lobar pneumonia often follow in the wake of an ordinary cold, so that responsibility for much major as well as minor illness might ultimately be laid at the door of the cold virus

Clinical picture

The onset of a cold may be remarkably sudden at a time when the sufferer has been in good health Sneezing, lacrymation, a dry, tickling throat, discharge of a clear, almost watery fluid from the nose and a need for extra handkerchiefs constitute the early symptoms. The nose becomes obstructed, and the discharge thickens and appears purulent during the next few days The throat is only slightly sore, nor is cough prominent, and after nasal symptoms have persisted for ten days or so, normal health is resumed The exact pattern of illness tends to depend to some extent on individual factors. In some there may regularly be a sore throat in the early phase of illness, and the voice may lose its tone or become actually hoarse. In others cough is experienced, and during the later phase of illness substernal soreness may be felt and sputum may

be raised. This is particularly so in bronchitic subjects, who take longer to recover from a cold than do normal individuals, largely because of the exacerbation of their cough and sputum. In others the nasal involvement, which always spreads to the accessory nasal sinuses to some degree, causes intermittent blocking in the drainage of these cavities, with resulting aching in the facial bones, and persistent purulent discharge for three or more weeks. In some children blockage of the Eustachian canal appears to occur in the course of the disease, so that earache may be experienced, and if a temporary injection of the drum is found a catarrhal otitis media has probably developed.

Though pyrexia is infrequent and never considerable, an elevation of temperature to between 99° and 100° F. may occur on the first day of a cold. Moreover, the individual feels miserable, may complain of chilliness, fatigue, slight headache or muscle aching. Such symptoms are not sustained in duration, however. It is doubtful whether the type of illness which begins with a brisk temperature reaction and ends after forty-eight hours or more in profuse running from the nose should properly be regarded as a cold. Epistaxis, or blood-streaking of nasal secretion, does, however, occur at times Physical signs are largely absent. The external nares are reddened, and the nasal mucosa engorged. Those subject to herpes labialis develop vesicles on the lips or face soon after the onset of a cold The fauces are not usually frankly abnormal, though dilatation of large vessels and some swelling of the adenoid tissue on the pharyngea wall are common Post-nasal muco-pus may be seen behind th uvula. The chest shows no signs unless the individual has a chron respiratory tract condition or is about to develop an attack of bronchitis In the latter case rhonchi or râles may be heard.

Ætiology and bacteriology

Although Kruse (1914) and Foster (1917) showed that colds could be produced in human volunteers by the nasal instillation of filtered nasal secretion from persons with colds, and Dochez and his co-workers (1930) confirmed and extended these observations, little further progress has been made in the study of the virus concerned. Both in the U S A and in Britain extensive experiments have been made since 1946, in an attempt to discover a convenient method of cultivation of the virus in the laboratory. Success has been claimed by American observers (Pollard and Caplovitz, 1947; Topping and Atlas, 1947; Ward and Proctor, 1950) in experiments utilising the chick embryo and testing the subsequent materials on human volunteers

The work of the Common Cold Research Unit of the Medical Research Council at Salisbury (Andrewes, 1949; 1950) has failed in similar experiments to find evidence of survival of the cold virus beyond one generation in chick embryos. Extensive experiments with a variety of experimental animals have also failed to indicate survival of virus in these hosts. Chimpanzees were not used, but Dochez and co-workers (1930) had earlier shown that the higher apes are susceptible to human colds either by natural exposure or by direct inoculation. The tests carried out at Salisbury have largely consisted in the direct inoculation of human volunteers who have been under quarantine in strict isolation. A variety of materials has been tested. Arising from these experiments a number of facts has become obvious, mostly from experiments with nasopharyngeal washings from patients in the early stages of ordinary colds. Inoculated human volunteers, of whom about 60 per cent are normally susceptible, thus develop a mild syndrome consisting of initial roughness or soreness of the throat, serous and then mucopurulent nasal discharge, slight malaise and, uncommonly, fever. The incubation period is two or three days. The duration of symptoms is less than a week. Unfiltered or filtered nasal washings are equally infective, but direct instillation of materials into the nose is necessary, and if the washings are diluted considerably, negative results are obtained. Nasal washings are infective if collected shortly before symptoms of a cold appear, but the duration of the infectivity after the onset of symptoms is not known for certain.

The induced cold in human volunteers does not seem to be highly contagious even when tested by contact with other volunteers who have been segregated from the population for some weeks (Andrewes, Lovelock and Sommerville, 1951). In this experiment contact between the volunteers with induced colds and the would-be recipient was attempted in various ways, and although no spread occurred, some of the recipient volunteers later succumbed to colds after contact with an individual suffering from a naturally acquired cold.

The agent capable of giving rise to symptoms in volunteers is smaller than influenza virus, and may be between 20 and 50 mμ in diameter. It survives storage at −76° C. for two years, and at −10° C. for at least a month. There is no evidence as to whether serologically different strains exist. The effect of reinoculation of human volunteers with the agent was not practised at Salisbury, but the experiments made by the Commission on Acute Respiratory Diseases (1947), using material from a case of common cold, suggested a lack of immunity to reinoculation with the same virus three

weeks after a first inoculation. Nor was immunity induced by previous inoculation of material from cases of febrile catarrh or primary atypical pneumonia.

Finally, although exposure or incidents causing chilling are popularly believed to be important in the incitement of natural colds, no consistent influence on induced colds in volunteers was exerted by experimental chilling (Andrewes, 1950).

Extensive observations have been made concerning the naso-pharyngeal bacterial flora in cases of common colds. The surveys made at Manchester (Study of the Nasopharyngeal Flora, 1930) and in London (Straker, Hill and Lovell, 1939) both showed that no consistent change in the bacterial flora of the nose or throat occurs during the acute stage of a cold. Some increase in the frequency of recovery of pneumococci and *H. influenzæ* was observed during the second week in colds studied in London, and these findings may indicate the reason for the occasional suppurative complications of a cold.

Pathology and diagnosis of the common cold

There is practically no knowledge concerning the pathological changes which accompany the common cold, and so far no opportunity has arisen for examination of lesions induced in experimental animals. Vascular changes such as vasodilatation of the erectile tissue of the nose and œdema are known to occur because of the temporary effect of vasoconstrictor drugs on the nasal obstruction accompanying a cold. The nasal secretion in the early stages contains few cells, but later, polymorphonuclear cells appear, which are probably derived by diapedesis through the nasal epithelium. It is not known whether necrosis of the ciliated columnar cells occurs, as in the experimental lesions of influenza virus infection.

The differential diagnosis of the common cold is confined chiefly to conditions which are accompanied by nasal congestion such as are induced by chemical, meteorological or allergic influences. Exposure to irritant gases or to chilling followed by a hot, stuffy atmosphere may cause turgescence of the nasal mucosa, which never truly resembles a cold for more than a brief period. Hay fever or allergic rhinitis due to inhalation of pollens is, however, accompanied by symptoms closely simulating a cold. Maximum seasonal prevalence in the spring or early summer, conjunctival irritation and congestion, intense sneezing and relief by the administration of antihistamine drugs or by adrenaline may help to distinguish. Chronic stuffiness of the nose due to nasal polypi or accompanying

CHAPTER 12

DIFFERENTIAL DIAGNOSIS

THE problem of diagnosis of the virus infections of the respiratory tract has already been considered from the laboratory standpoint. It has been made clear that the discovery of the ætiological agents concerned in the various clinical syndromes depends either upon cultivation of these agents in the laboratory or upon serological tests. But there are two serious drawbacks to the wider diagnostic use of these tests. In the first place, the results are often retrospective, in the sense that the patient is well before the answers are available either because of the time needed for the identification of a virus or because a convalescent serum is necessary in order to compare the antibody levels at two different times. Secondly, the work is of a highly technical character which is often beyond the powers of a routine diagnostic laboratory. Therefore the diagnosis of individual illnesses met with in clinical practice cannot often be based upon exact laboratory procedures, however informative these may be from the standpoint of epidemiology.

It must be obvious, therefore, that in the acute stage of illness diagnosis still depends upon a careful clinical appraisal. This will require to be based upon the symptoms and signs which are found and on other relevant information obtained concerning the health of close contacts of the patient. The detailed nosology of the various clinical syndromes has in fact been stressed in the earlier chapters of this book precisely for this reason, because practitioners are still called on to exercise clinical care and discrimination if they desire to make an accurate diagnosis

It is best now to approach the problem of diagnosis from an opposite standpoint to that hitherto adopted. Let us consider the chief clinical forms in which these virus infections of the respiratory tract present themselves, in order to discuss more adequately their differentiation from other conditions. To this end, it will be necessary to use names for these forms which are devoid of an ætiological significance, in order to emphasise the outstanding features of the various clinical patterns.

(1) Pyrexia of unknown origin (P.U.O.)

Under this heading can be included all illnesses characterised by pyrexia of either short or long duration and with an absence of

localising or distinctive signs such as rashes, obvious foci of suppuration and so on. All the virus infections of the respiratory tract except the common cold may present in this relatively undistinctive manner. And so also may certain other virus infections or conditions such as pyelitis, enteric fever, tuberculosis, brucellosis, subacute bacterial endocarditis, infective hepatitis, Weil's disease, glandular fever, the leukæmias, Hodgkin's disease and the reticuloses in the early stages. Confusion between these latter conditions and the virus infections is only really likely in the early stages, before the development of localising signs which will make the true diagnosis obvious.

First let us consider the symptoms and signs in the pyrexias due to the respiratory tract infections which aid in their mutual differentiation. The onset will usually be abrupt in the case of influenza, psittacosis and Q fever, less abrupt, or even insidious, in febrile catarrh and primary atypical pneumonia. The symptoms in all the conditions during the first two days of illness are likely to include headache, shivering, malaise and muscular pains. Reliance cannot be placed upon the presence or absence of particular symptoms. Muscular aching in the limbs or back is a common symptom of influenza, but it is not invariable at any age, and it is frequently absent in young adults. Moreover, it is also experienced in febrile catarrh, psittacosis and Q fever in a proportion of cases not significantly different from influenza. It is the variation in the individual clinical illnesses in all these conditions which is responsible for their confusion in the early stages. Symptoms arising from the respiratory tract, though often present at an early stage, may not be definite enough to indicate that this tract is specifically affected. For instance, dry cough is almost invariable in influenza and febrile catarrh, but less uniformly experienced in psittacosis and Q fever.

Help may come to the diagnostician as time passes. For by the third or fourth day of illness in cases of influenza and febrile catarrh pyrexia should be lessening or have abated entirely, whereas it is more likely to persist beyond this stage in primary atypical pneumonia, psittacosis and Q fever. If fever still persists on the fifth day of illness of an attack of influenza or febrile catarrh, cough and sputum are nearly always present, and with these symptoms the involvement of the respiratory tract becomes obvious. Usually also there are obvious physical signs in the chest, such as râles or altered breath-sounds, which will draw attention to the chest and suggest the desirability of a chest X-ray.

Radiography of the chest towards the end of the first week of the



various virus infections of the respiratory tract is therefore most *helpful*. In influenza and febrile catarrh, though there may be obvious physical signs in the chest, the lung-fields are radiologically clear unless a bacterial complication has supervened. But the majority of patients with primary atypical pneumonia, psittacosis or Q fever show radiological changes in the lungs by the end of the first week of illness. The actual appearance of the X-ray opacities in pulmonary complications of the virus infections may be difficult to distinguish from bacterial pneumonia, or they may at once suggest the diagnosis. But once a chest lesion has been demonstrated the case ceases to be one of P.U.O., and differentiation from other pyrexial diseases becomes much more obvious Before considering the latter conditions in greater detail it may be as well to point out the negative findings in the virus infections of the respiratory tract during the early stages of illness, which may be also of differential value.

The height of the fever in influenza and febrile catarrh rarely exceeds 103° F. and if a temperature of 104° is reached, it is usually *maintained for only a few hours. The pulse rate is usually raised* in proportion to the height of the pyrexia, or is relatively slow. The *respirations, though rapid in rate, are not distressed* as in the tachypnœa of a bacterial pneumonia. The actual degree of illness *is slight in all the virus infections compared with systemic conditions* such as enteric fever, but an exception must be made for the aged *person smitten with influenza, who may be extremely prostrated* and ill. Another negative character in the virus infections is the absence *of a polymorphonuclear leucocytosis, so that the finding of* a leucocytosis will at once lead to a search for some other condition or for a bacterial complication.

If doubt concerning the diagnosis still exists after a careful clinical examination has been made, *the epidemiological* background of the case should always be explored. The existence of an explosive outbreak of pyrexial cases *at once makes the situation much* more obvious. For, apart from outbreaks of food-poisoning and enteric fever, in which the contacts are likely to have been infected from a common source and to have alimentary symptoms, explosive epidemics are more likely to be due to *influenza, febrile catarrh* or Q fever than to any of the other pyrexias Often, however, the family practitioner sees only a small portion of an *outbreak, and* it is then that the numbers of smitten persons in a family becomes important. Influenza is of course *the febrile condition with a rapid*, almost simultaneous involvement of most members in a household It is

and sometimes seen as an associated condition during an epidemic of influenza, soon reveals its identity by the intensity of the diarrhœa. It is likely that a good many of the illnesses termed 'gastro-intestinal flu' are actually due to *Sh. sonnei* However, there is the other condition of gastro-enteritis of unknown ætiology which is endemic or epidemic in incidence and which may or may not be due to bacterial or virus agents. It is certainly unwise to regard any illness in which diarrhœa is prominent as being due to a virus infec- [illegible]

gastro-enteritis has been discovered, then the relationship of the respiratory infection which may accompany this disease will become evident For the present, diarrhœa with or without respiratory symptoms is an indication for bacteriological investigation of the stools.

Tuberculosis Everyone can cite the case of pulmonary tuberculosis, or even of miliary tuberculosis which was first diagnosed as influenza But the onset is rarely sudden and previous slight malaise, or a cough, or some chest pain occur prior to the development of pyrexia. There is no golden rule in the diagnosis of pulmonary tuberculosis, particularly in a young adult, except to consider the possibility and to obtain an X-ray of the chest as soon as is practicable. There is certainly no necessity for there to be sputum either mucopurulent or with hæmoptysis, nor may the sedimentation rate be high, but cough is almost invariable, even in the early case. Reliance cannot be placed on abnormal signs in the chest, though if signs at the apices are found, then the possibility of tuberculosis is, of course, increased.

Respiratory symptoms are frequently absent in miliary tuberculosis e [illegible] ation of an olc [illegible] the degree o [illegible] the chest, and perhaps splenomegaly will make the diagnosis clear. In any case of continuing pyrexia in a young adult enquiry should be made as to a possible contact with a case of tuberculosis in the home or at work, and investigation of the sputum or of gastric washings for acid-fast bacilli should be pursued in all cases in which the chest X-ray is at all suspicious

The early diagnosis of tuberculous meningitis has become of paramount importance now that treatment with streptomycin has become available In the case of tuberculous meningitis there is

usually a period of vague illness and perhaps personality changes before the onset of headache, vomiting and signs of meningitis. Lumbar puncture is essential for the diagnosis, and if a child or young adult who is pyrexial also has definite neck stiffness, then an examination of the cerebrospinal fluid is certainly necessary. The meningism which occasionally accompanies an acute infection such as an apical pneumonia rarely persists for more than a day or so, and should not cause confusion. The discovery of an increased number of cells in the C.S.F. does not, of course, mean that the diagnosis is one of tuberculous meningitis, for there are many relatively benign causes of a pleocytosis. But none of the acute virus infections of the respiratory tract under discussion is normally accompanied by a change in the C.S.F. Decrease in the chloride or sugar content of the C.S.F. is evidence in favour of tuberculous rather than of benign lymphocytic meningitis.

Brucellosis As a cause of prolonged pyrexia with few localising signs, brucellosis has a definite place in the differential diagnosis of the conditions under consideration. Splenomegaly, arthritic signs or pains in the joints and a leucopenia of 4,000 cells per cu mm or less are helpful to the diagnosis. A rising titre of agglutinins for brucellæ in the serum or cultivation of brucellæ from the blood are necessary for positive diagnosis of this condition.

Subacute bacterial endocarditis. The development of fever in a subject already known to suffer from rheumatic or congenital heart disease, such as patent ductus arteriosus, rarely causes confusion with influenza. But the cardiac signs are inconspicuous in some cases of subacute bacterial endocarditis, and unless care is taken to look for finger clubbing, splinter hæmorrhages in the finger-nails or petechiæ in the conjunctivæ, splenomegaly, or red cells and casts in the urine, the true diagnosis may be missed The fever is likely to be intermittent and perhaps accompanied by rigors, constitutional symptoms are slight, the cardiac murmurs may change in intensity, and blood culture will reveal the true diagnosis

Infectious hepatitis. This will only cause confusion in the pre-icteric stage, and once jaundice has appeared the cause of the pyrexia will be obvious.

Weil's disease. The usual clinical picture with jaundice is unlikely to be a source of confusion, but there is another variety with meningism or actual meningitis which may be more confusing The presence of cells in increased numbers in the C.S.F. makes a virus infection of the respiratory tract unlikely. The diagnosis of Weil's disease depends on the demonstration of a rising titre of agglutinins

and sometimes seen as an associated condition during an epidemic of influenza, soon reveals its identity by the intensity of the diarrhœa It is likely that a good many of the illnesses termed 'gastro-intestinal flu' are actually due to *Sh. sonnei* However, there is the other condition of gastro-enteritis of unknown ætiology which is endemic or epidemic in incidence and which may or may not be due to bacterial or virus agents. It is certainly unwise to regard any illness in which diarrhœa is prominent as being due to a virus infection belonging to the respiratory group. Diarrhœa is not a normal symptom of influenza virus infection, febrile catarrh, primary atypical pneumonia or Q fever When the causal agent or agents of epidemic gastro-enteritis has been discovered, then the relationship of the respiratory infection which may accompany this disease will become evident. For the present, diarrhœa with or without respiratory symptoms is an indication for bacteriological investigation of the stools.

Tuberculosis. Everyone can cite the case of pulmonary tuberculosis, or even of miliary tuberculosis which was first diagnosed as influenza But the onset is rarely sudden and previous slight malaise, or a cough, or some chest pain occur prior to the development of pyrexia. There is no golden rule in the diagnosis of pulmonary tuberculosis, particularly in a young adult, except to consider the possibility and to obtain an X-ray of the chest as soon as is practicable. There is certainly no necessity for there to be sputum either mucopurulent or with hæmoptysis, nor may the sedimentation rate be high, but cough is almost invariable, even in the early case Reliance cannot be placed on abnormal signs in the chest, though if signs at the apices are found, then the possibility of tuberculosis is, of course, increased.

Respiratory symptoms are frequently absent in miliary tuberculosis except when spread has occurred as a result of the activation of an old lesion such as a cavity, but the high swinging fever, the degree of illness of the patient, the radiological appearances in the chest, and perhaps splenomegaly will make the diagnosis clear. In any case of continuing pyrexia in a young adult enquiry should be made as to a possible contact with a case of tuberculosis in the home or at work, and investigation of the sputum or of gastric washings for acid-fast bacilli should be pursued in all cases in which the chest X-ray is at all suspicious

The early diagnosis of tuberculous meningitis has become of paramount importance now that treatment with streptomycin has become available In the case of tuberculous meningitis there is

usually a period of vague illness and perhaps personality changes before the onset of headache, vomiting and signs of meningitis Lumbar puncture is essential for the diagnosis, and if a child or young adult who is pyrexial also has definite neck stiffness, then an examination of the cerebrospinal fluid is certainly necessary The meningism which occasionally accompanies an acute infection such as an apical pneumonia rarely persists for more than a day or so, and should not cause confusion. The discovery of an increased number of cells in the C.S F. does not, of course, mean that the diagnosis is one of tuberculous meningitis, for there are many relatively benign causes of a pleocytosis But none of the acute virus infections of the respiratory tract under discussion is normally accompanied by a change in the C.S F. Decrease in the chloride or sugar content of the C S F. is evidence in favour of tuberculous rather than of benign lymphocytic meningitis

Brucellosis As a cause of prolonged pyrexia with few localising signs, brucellosis has a definite place in the differential diagnosis of the conditions under consideration Splenomegaly, arthritic signs or pains in the joints and a leucopenia of 4,000 cells per cu mm or less are helpful to the diagnosis A rising titre of agglutinins for brucellæ in the serum or cultivation of brucellæ from the blood are necessary for positive diagnosis of this condition

Subacute bacterial endocarditis The development of fever in a subject already known to suffer from rheumatic or congenital heart disease, such as patent ductus arteriosus, rarely causes confusion with influenza. But the cardiac signs are inconspicuous in some cases of subacute bacterial endocarditis, and unless care is taken to look for finger clubbing, splinter hæmorrhages in the finger-nails or petechiæ in the conjunctivæ, splenomegaly, or red cells and casts in the urine, the true diagnosis may be missed The fever is likely to be intermittent and perhaps accompanied by rigors, constitutional symptoms are slight, the cardiac murmurs may change in intensity, and blood culture will reveal the true diagnosis

Infectious hepatitis. This will only cause confusion in the pre-icteric stage, and once jaundice has appeared the cause of the pyrexia will be obvious

Weil's disease The usual clinical picture with jaundice is unlikely to be a source of confusion, but there is another variety with meningism or actual meningitis which may be more confusing The presence of cells in increased numbers in the C S F makes a virus infection of the respiratory tract unlikely The diagnosis of Weil's disease depends on the demonstration of a rising titre of agglutinins

to leptospiræ in the serum, or on the recovery of the organism by blood culture.

Glandular fever, Hodgkin's disease, reticuloses and the leukæmias. None of these conditions should be confused with the virus infections of the respiratory tract. Enlargement of superficial lymph nodes or of the spleen or liver occurs eventually, and the cause of the pyrexia then becomes obvious. Glandular fever is the most likely to cause diagnostic difficulty because of its protean manifestations. The demonstration of a monocytosis in the blood is essential The Paul–Bunnell reaction may or may not become positive

Pyrexial states due to other virus infections It is necessary to draw attention to the fact that many virus infections other than those under consideration may cause temporary diagnostic difficulty and be labelled as P.U.O. For instance, the early stage of small-pox before the appearance of the rash is accompanied by headache, back-ache and shivering; the same may be said for the other exanthemata Sand-fly fever and dengue fever in those areas where the conditions are endemic are closely similar to influenza. Poliomyelitis in the pre-paralytic stage may be dismissed as 'flu, and Bornholm disease may likewise be misdiagnosed if adequate attention is not paid to the localised abdominal or shoulder-tip pain. The syndrome of herpangina (Huebner and others, 1951), which has been shown to be due to infection by the Coxsackie group of viruses, is particularly confusing, in that there is fever, general illness, headache or muscular aching and a sore throat There is, however, a vesicular rash upon the soft palate with a superficial resemblance to herpetic vesicles, and this is responsible for the name. The maximum incidences of both poliomyelitis and of Coxsackie virus infection are in the autumn rather than in midwinter, but they should not be forgotten when considering the diagnosis of individual pyrexial illnesses.

Finally, benign lymphocytic meningitis due to mumps or polio-myelitis or of unknown ætiology may be confusing until the demonstration of neck stiffness leads to a lumbar puncture. Cells in the cerebrospinal fluid will make the diagnosis clear.

An illustrative outbreak of P U O The following account (Stuart-Harris, 1945) of an outbreak of Q fever in British troops witnessed during the second world war may serve to illustrate the diagnostic difficulties of virus infections of the respiratory tract presenting as predominantly pyrexial illnesses

'There were sufficient numbers (40 or more in a week) for the incident to be described as an outbreak, but the cases were scattered throughout many units, so that the incidence was sporadic rather

than epidemic. The fever lasted from five to ten days on the average during which time the men were quite ill with general symptoms such as headache and muscular pains. Although there was little coryza or sore throat, most patients had cough and pain in the chest often as an initial symptom. There was often a history of exposure to cold or damp before the onset. The geographical location (Italy) of these patients [illegible] ill led to the exclusion of malaria by repeated examination [illegible] blood films before the cases were described as [illegible] A solitary patient admitted with fever, [illegible] symptoms was suspected of typhus. He was [illegible] had a few pink macules on the abdomen, but no [illegible] enlargement of the spleen. The rash did not develop [illegible] Felix reaction remained persistently negative and [illegible] chest showed a picture suggesting atypical pneumonia.

The majority of the patients exhibited areas of [illegible] chest, and sometimes there was bronchial breathing [illegible] or pleural friction. Radiological examination of the chest [illegible] pneumonic areas of small size in most patients, but [illegible] leucocytosis, and sulphonamides gave no therapeutic response [illegible] absence of pathogenic bacteria from the sputum and the [illegible] cold agglutinins to develop in the serum could not at that time be explained. It was then that Robbins demonstrated the [illegible] of Q fever in similar cases in American troops in Italy and [illegible] study of cases in British troops indicated that these also were due to *R burneti*. Without the use of radiology and of laboratory assistance this outbreak would perforce have been labelled one of P U O or 'grippe' or febrile catarrh. As it was, the significance of exposure of the men to cattle-fodder and excreta while fighting in the open and sleeping in barns was entirely missed.

In this outbreak, the evidence of involvement of the respiratory tract rapidly led to abandonment of alternative diagnoses such as enteric fever, typhus or malaria, but there is no doubt that much help was afforded by the simultaneous admission of the group of patients to hospital. The bizarre case quoted thus failed to arouse the difficulty which would have occurred if this patient, and this patient only, had been met in practice.

(ii) Febrile sore throat

This title is used rather than that of pharyn[illegible] because sore throat and fever are found in many con[illegible] those locally affecting the fauces. The main diffi[illegible]

is between febrile catarrh including non-streptococcal pharyngitis, streptococcal sore throat and glandular fever. At the same time, influenza in children may cause sore throat, and as the headache and muscular pains are often so trivial in the young, pharyngitis may be diagnosed. The diagnosis between febrile catarrh and streptococcal sore throat is considered on page 135. The point should perhaps be made that streptococcal infection occasionally presents as a pyrexia for some hours before sore throat and pharyngitis are experienced. Glandular fever in its anginose form may cause considerable confusion with either febrile catarrh or streptococcal infection. The onset of illness is relatively gradual; there may be headache, muscular pains and shiveriness; glandular enlargement may be slight initially and the throat may be normal. Sore throat may later become prominent and the fauces may show ulceration and a greyish slough. There may be considerable dysphagia, and at this stage the cervical lymph nodes are usually enlarged. The leucocyte count will show increased numbers of lymphocytes and monocytes, but the polymorphonuclear count may be reduced to neutropenic levels A point of distinction from febrile catarrh with an exudate on the throat is that the larynx is often involved in the latter, but not in glandular fever. The leucocyte count differentiates the two conditions. The discovery of enlarged lymph nodes in regions other than the neck or of splenomegaly would at once suggest glandular fever or other disease of the hæmopœitic system.

(iii) 'Tracheitis' and 'bronchitis'

Unlike the subject with a pyrexia of unknown origin, the case of 'tracheitis' is obviously one of respiratory tract disease. The chief symptom is a frequent and irritating cough, accompanied by substernal pain on coughing or by a raw burning feeling beneath the sternum. Sputum, if present, is not usually abundant. Febrile 'tracheitis' is one of the forms of presentation of febrile catarrh, and the pharynx and larynx are usually involved as well, thus giving a sore throat and hoarseness to the voice. Influenza does not [illegible] present in this way. The laryngotracheitis of infants is [illegible] by various [illegible] se arises [illegible] tionship in infants, and it is possible that [illegible] to the virus infections of the respiratory tract. It is, of course, a much more dramatic condition than the febrile catarrh of adults; there is grave illness, stridor and considerable respiratory distress Treatment with antibiotics such as chloramphenicol,

aureomycin or terramycin has greatly changed the prognosis and mortality.

The distinction between trach[illegible]

[illegible] the lungs, so that an X-ray examination will distinguish both of these from an atypical or bacterial pneumonia The case with predominant signs of bronchitis is a problem from the standpoint of ætiology. Instances have been given already of cases of influenza with bronchitis, and similar cases occur during outbreaks of febrile catarrh. Probably bronchitis can at times be induced by any of the viruses capable of attacking the respiratory tract, but there is no doubt concerning the importance of the individual human constitution in determining the clinical picture The difficulty is greatest in the sporadic case of fever, cough and sputum, with either diffuse rhonchi or diffuse râles in the chest. When rhonchi predominate, there may be dyspnœa and respiratory difficulty The physical signs suggest bronchospasm, and differentiation from an attack of [illegible] perhaps with sputum, [illegible] n order to eliminate

[illegible] chitis whenever they experience colds, and a good many of these 'grow out of' their weakness as they age But it is not at all unlikely that some of these individuals are predisposed by their earlier experience and perhaps by minor anatomical damage to the bronchial tree, so that when they later suffer from attacks of influenza or of febrile catarrh, their clinical reaction indicates involvement of the bronchi once again The differential diagnosis from bronchiectasis is helped by the frequent occurrence of pain of pleural origin during exacerbations of bronchiectasis with superadded bacterial infection. Bronchitis is not accompanied by pleural pain, though a 'tightness of the chest' or substernal pain is common. Persistence of sputum and cough in between acute attacks of so-called bronchitis is another pointer to bronchiectasis, and should lead to radiological examination and bronchography.

Probably the danger of labelling a patient as 'bronchitis' is that a more serious condition, such as pulmonary tuberculosis, is thereby missed, and examination of the sputum must always be carried out in cases where sputum or physical signs persist for more than a few days

Another cause of difficulty is that some systemic illnesses, such as

enteric fever, are accompanied by signs of bronchitis in the early stages of illness.

(iv) The case of pneumonia

A good deal has already been said in Chapters 3 and 8 on the subject of the differentiation of the various types of pneumonia When an outbreak of respiratory infection is in progress there is little likelihood that cases of actual consolidation of the lungs will be missed. The history of an influenzal illness prior to the development of sharp pleural pain, increased cough and sputum and dyspnœa will suggest that pneumonia has developed as a complication of influenza. The likelihood is that this is a bacterial pneumonia which will respond to chemotherapy or antibiotics. The only danger is that the organism may be a *Staphylococcus pyogenes* and that the fact that therapy must therefore be pursued energetically may not be realised early enough

If the history is that of a clear-cut attack of pneumonia ensuing perhaps on the heels of a cold, the likelihood of a bacterial infection such as that produced by the pneumococcus is considerable. The signs in the chest are usually frank, the sputum is rusty and viscid, there is a dense radiological opacity and the leucocytes are usually increased The vast majority of such illnesses respond either to sulphonamides or to penicillin within thirty-six hours or less of the commencement of therapy.

It is often the failure of chemotherapy to influence the illness which points to the fact that the condition is not simply a bacterial pneumonia, or even a bacterial complication of a virus infection Atypical pneumonia owed its recognition long ago to a realisation that in this syndrome orthodox treatment may not succeed in restoring the patient to normal health. The danger nowadays is rather that when sulphonamides or penicillin fail, the clinician may immediately jump to the conclusion that the case is one of 'virus pneumonia', and may fail to appreciate the fact that some cases of bacterial pneumonia, such as those due to pneumococcus Type III, *Staphylococcus pyogenes*, Friedlander's bacillus, and even the tubercle bacillus, are relatively or completely unresponsive to treatment with sulphonamides or penicillin in normal doses The failure of therapy in a case of pneumonia should lead, therefore, to a prompt and adequate bacteriological examination of the sputum and to radiological examination of the chest. If the patient is severely dyspnœic and dense radiological opacity exists in the chest, then the diagnosis is still one of probable bacterial pneumonia, rather than of a virus

infection. If bacteria cannot be demonstrated in the sputum, the possibility of infection by the psittacosis group of viruses should be explored by tests for this infection. If the radiological findings suggest an atypical pneumonia, then search should be made as outlined in Chapter 8. Treatment with antibiotics such as aureomycin, chloramphenicol or terramycin is more likely to be successful in atypical pneumonia than is the use of penicillin or streptomycin, and this subject is discussed again in Chapter 14

Finally, due care must be taken that other causes of pain in the chest, cough, sputum and dyspnœa are not forgotten Pulmonary embolism is often mis-diagnosed as pneumonia, and so also is a bronchial carcinoma The development of suppuration within a consolidated area may, of course, be due to infection by the staphylococcus or Friedländer's bacillus, but abscess formation is also common in carcinoma distal to a blocked bronchus Pleural effusions which develop in patients despite treatment by antibiotics also complicate the clinical picture, even if they are sterile on culture. The differential diagnosis of the various varieties of bacterial and virus pneumonias calls for exhibition of the greatest degree of clinical acumen aided by adequate investigation and follow-up. The fact that bronchial carcinoma is often missed at its earliest stage of presentation, when a bacterial pneumonia has occurred distal to the affected bronchus, is a cause for exercise of much caution before use of the words 'atypical pneumonia' Adequate radiological control of the process of resolution is essential in the avoidance of this error.

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have occasionally been found [illegible]
others, 1949), and the ing[illegible]
be the cause of human inf[illegible]
possible against the reserv[illegible]
economic loss. The size of the problem of the human disease in Great Britain is probably not large, and does not warrant the destruction of infected herds. The possibility of inducing artificial resistance in cattle in order to prevent the perpetuation of infection within a herd seems worthy of exploration.

The mode of transmission

All the viruses of the respiratory tract considered in this book are spread by means of the air. As in the case of ordinary bacteria, they may be transmitted as dried materials present in dust which are re-suspended into the air by dust-raising procedures such as shaking or sweeping. Or they may be present in the large and small droplets exhaled in the breath or expelled from the nose or throat during acts such as coughing, sneezing or talking. Large droplets follow a relatively short trajectory after expulsion from the mouth, and can only pass, therefore, from one person to another during periods of close contact. The minute aerosol droplet-nuclei, which are invisible, can, on the other hand, remain suspended in the atmosphere for long periods, and can render the air infectious even after infected persons have left the room concerned. It is possible, even though aerial hygiene is still in its infancy, to formulate methods of attack against each of these three materials which may transmit viruses through the air. Briefly, dust-laying for dusts, barriers and handkerchiefs for large droplets and mists or vapours containing disinfectants for the droplet-nuclei can each or all be employed, and experimentally have been shown to be effective in diminishing aerial contamination by bacteria. But the methods vary in their degree of effectiveness against different organisms, and in any case it is necessary first to decide which of the various air-borne materials furnish the chief mode of transmission of the viruses. Unfortunately, the basic data for this decision are extremely meagre, and controversy exists regarding their interpretation

The influenza virus has been recovered from dust, and has been shown to remain viable for a week or more at room temperature (Edward, 1941) It has also been recovered from the atmosphere after infected fluid has been atomised and dispersed into the air. Infection has been conveyed from an infected ferret to a normal animal over a distance of 5 feet in almost still air, and to an animal

located several feet vertically above. Successful transmission of the virus has also been obtained in ferrets by using closed conduits which interposed a trap for coarse droplets, so that only droplet-nuclei remained to carry the virus (Andrewes and Glover, 1941). It is therefore clear that an infected atmosphere can act as a vehicle for the influenza virus, but it is not known whether such indirect contagion is the principal mode of transmission during an epidemic. Indeed, the few epidemiological data (Hare and Mackenzie, 1946) which throw light upon spread during an epidemic have tended to suggest that it is intimate contact with the human person which is chiefly responsible for transmission. Infected persons, either with or without clinical disease, can spread the virus by shedding dried particles from their clothes or handkerchiefs or by emitting droplets to those in immediate contact with them.

Still less is known concerning the spread of the viruses of colds, febrile catarrh or primary atypical pneumonia. It is known that fomites can act as a source of infection for colds in certain circumstances, and the person with a 'streaming cold' almost certainly infects his face, hands and clothes during the acute stage of the infection. Observations on the higher apes at the London Zoo suggest that a glass screen not reaching to the ceiling, and interposed between the apes and public, is sufficient to protect the animals from human colds. This is evidence in favour of large rather than small droplets as a source of contagion, but the experiments carried out on human volunteers have not decided the issue at all conclusively.

In Q fever and psittacosis, however, though the acquisition of infection is almost certainly by means of contaminated air, the likelihood is that dust containing desiccated virus particles is the actual *milieu* for conveyance of the rickettsiæ and viruses to man. As transmission of disease from man to man does not normally occur in either of these infections, it is obvious that general methods of control of air-borne infection hardly apply in these special instances, except possibly in laboratories where work upon the causative agents is in progress.

But in the case of all the other infections under consideration, a rational scheme for the diminution of air-borne infection would have the advantage of a relatively non-specific approach. A method which was effective against one of the viruses might also be effective against the others, and this would obviate the development of an individual approach to each infection. Unfortunately the achievements so far have been largely confined to experiments which have demonstrated the possibility of sterilising the air rather than that of

diminishing the incidence of infection. The reader is advised to consult the pioneer studies of Wells and Wells (1938, 1943) and the Special Report to the Medical Research Council by Bourdillon, Lidwell, and Lovelock (1948) for details of the physical and engineering problems which exist in this field. The methods of approach which have been developed can hardly be applied to individuals living in their own homes and utilising public transport. They would be particularly useful in communities living in a residential home or barracks and enjoying communal messing, canteens and recreation rooms. They can also be applied to a hospital population

Thus, dust-laying by the use of mineral oil applied to floors and blankets was shown by van den Ende and co-authors (1940, 1941) to reduce bacterial pollution of the air occurring as a result of floor-sweeping and bed-making. Applied in a hospital ward, the oiling technique has been shown to diminish cross-infection by hæmolytic streptococci (Wright and co-authors, 1944), but experience has not been uniformly favourable (Begg and co-authors, 1947). Chemical disinfection by hypochlorites, the glycols, lactic or α-hydroxy-acids, and physical methods of disinfection by ultra-violet light, can act against air-borne droplets and droplet-nuclei. Chemicals are dispersed into the air either as vapours or as a mist of aerosol droplets. They are certainly actively bactericidal against droplet-nuclei, but are less effective against dust. Their activity may be altered by factors such as the relative humidity of the air. Ultra-violet light is also more effective against air-borne droplets than against contaminated dust, but its effect is also modified by the relative humidity of the air Mechanical barriers, such as masks and handkerchiefs, are useful in limiting the direct transmission of droplets from man to man Unfortunately, masks are not tolerated well if worn for long periods. A proper hygienic appreciation of the role of the handkerchief during sneezing and coughing would provide a useful practical approach to this problem Disinfectants can also be incorporated into handkerchiefs (Dumbell and Lovelock, 1949), but the use of this method has not been explored widely. Finally, an increased rate of turnover of the air of rooms employed communally by large numbers of individuals or of the air of bedrooms by properly arranged ventilation is an important basic method for the reduction of the spread of infection by the air.

Present significance of air hygiene

The methods described above have been used experimentally in hospital wards, in clinics housing babies and infants, in schools, in

Service barracks and in industrial establishments In all of these environments claims have been made by individual workers or teams of workers that a worth-while reduction of respiratory disease has sometimes been attained. Yet on analysis it is clear that the experiments have often failed under precisely the conditions during which prevention is desired Thus, although the incidence of endemic respiratory disease may have been lowered, outbreaks such as influenza A have caused as high an incidence in populations subjected to methods of dust-laying or air-disinfection as in control groups (Langmuir and co-workers, 1948). Considering the magnitude of the trials made both in this country (Bourdillon and others, 1948) and in the U.S.A. by the U.S Commission on Acute Respiratory Diseases (1947), and by the U.S. Navy (Schechmeister and Greenspan, 1947; Willmon and others, 1948, Langmuir and others, 1948), the results achieved must be regarded with disappointment Nor is it clear why the experiments have sometimes failed completely, except that the air is a universal medium essential to man, and protection can only be applied during a very limited period of the day or night. The need is clearly that continued research should be made into the fundamental problems of air-borne infection, and into the engineering problems of the application of hygiene to the air The opposing viewpoints that the goal is one of dust control on the one hand (Loosli, 1948) or of disinfection of the air on the other (Wells, 1945) still exists The type of study carried out on the populations of entire villages, such as that reported by Wells and Holla (1950) from rural areas in New York State, should ultimately settle the controversy.

Protection of the individual hosts

The development of a state of resistance of the human respiratory tract to attacks by the various viruses would undoubtedly control infection by these agents. Yet, though work has been pursued upon immunization from the earliest days of study of the influenza viruses, there are some important theoretical handicaps to its use The fact that immunization is a specific process means that any protection which it might afford is also highly specific Moreover, artificial methods of inducing immunity are not usually more efficacious than the immunity induced by natural processes, and the natural history of colds and influenza suggests only a temporary immunity after each attack. Again, immunization against a disease such as influenza would hardly be likely to affect the course of an epidemic unless simultaneous protection could be afforded to very large numbers of

individuals Other possible ways of producing resistance, such as by passive immunization or by the induction of local changes in the cells of the nose, or by chemotherapeutic compounds, therefore require consideration.

Immunization against influenza

A considerable body of knowledge now exists in regard to the possibilities and limitations of immunization against influenza The basis of immunization is the experimental demonstration that antibodies can be produced by the parenteral inoculation of animals or of humans with living or killed (inactivated) preparations of influenza viruses A or B, and antibodies capable of neutralizing influenza virus are believed to be of considerable importance in the determination of immunity to infection, as already pointed out in Chapter 6. Further, the problem of immunization of man is essentially that of altering a state of waned immunity to one of full resistance, for all adults have experienced at least one attack of influenza Experiments on ferrets suggest that restoration of antibodies is more likely to be efficacious in inducing immunity than is the primary stimulation of antibody formation in a previously uninfected host. However, this observation may be the result simply of the greater quantity of antibody induced by the process of immunization in previously infected animals, for it is probable that a certain level of serum antibodies is essential if the nasal and bronchial mucous membranes are to benefit by being bathed in an environment inimical to the virus.

There was good experimental evidence in favour of the view that artificial immunization might be successful in man even before field trials were undertaken. But the practical demonstration by Stokes and Henle (1942) that human volunteers who had been injected intramuscularly with inactivated virus A vaccines were able subsequently to resist exposure to inhaled living virus A was a landmark The detailed description of these experiments on human volunteers [illegible] indicated

months prior to challenge by inhalation of [illegible] extensive experiments on human volunteers were recorded by Francis and others (1943) and by Salk and co-authors (1945a). Though significant protection was demonstrated after subcutaneous immunization either with influenza virus A or virus B vaccines, it appeared that the best results were obtained if the vaccine was given within two to four weeks of the challenge by inhalation of living virus.

These experiments were followed by the report of the Commission on Influenza (1944) on the successful result of the first extensive field trials of influenza virus vaccines during an epidemic of influenza A. The incidence of clinical influenza during this outbreak was 2·22 per cent among 6,263 students immunized previously with formalinised influenza virus A and B vaccine prepared from infected eggs, compared with that of 7·11 per cent in 6,211 comparable controls (Table 19). The outbreaks occurred in most of the experimental camps within two to four weeks of the date of immunization, but in a group in California the interval was much longer, and the protective effect of the vaccine was also less than elsewhere. This field study satisfied statistical requirements in regard to the comparability of the two groups of immunized individuals and controls, and has been recognised all over the world as a classical experiment which demonstrated that artificial immunization against influenza A is possible.

In the succeeding years, Francis, Salk and Brace (1946) and Hirst and others (1947) recorded suggestive evidence of the efficacy of a similar mixed formalinised virus A and B vaccine during an epidemic of influenza B. In these experiments groups of immunized Army students experienced a clinical incidence of from one-ninth to one-twenty-fifth that encountered in neighbouring unimmunized Naval students. But, as the two groups of immunized and unimmunized students were separately housed, the experiments hardly fulfilled the requirements of statistical comparability, and the evidence was therefore suggestive rather than conclusive.

In the spring of 1947, however, groups of immunized students in the U.S.A. were exposed to an outbreak of influenza three to four months after vaccination with mixed influenza virus A and B vaccines similar to those previously used. No differences in attack rates were now discerned between the immunized and control groups at Michigan (Francis, Salk and Quilligan, 1947), at Yale, or in the U.S. Army (Smadel, 1947), although the infection was shown to be due to influenza virus A. Similar results were reported by Sigel and others (1948) and Loosli and others (1948). But when the strains of virus recovered from the various American outbreaks in 1947 were subjected to detailed antigenic analysis, it was found that sharp serological differences existed between these and the strains of influenza virus A used in the manufacture of the vaccine. The latter strains belonged to the classical PR8 group of viruses, such as had been encountered in the field from 1936 to 1943, but the new strains were the first of the influenza A prime viruses identified in outbreaks in the U.S.A. (see Chapter 5). Tests made on the sera from persor

TABLE 19

Influenza Vaccination

Unit	Date of vaccination	Period of epidemic	Number of subjects.			Cases of influenza		Percentage incidence.		Percentage distribution total cases.	
			Vaccinated	Control	Total.	Vaccinated	Control.	Vaccinated	Control	Vaccinated	Control.
Cornell .	9 Nov.	23 Nov.–18 Dec									
N Y Medical Schools .	26 Oct–4 Nov.		498	484	982	15	43	3.01	8.86	26	74
Princeton .	2 Nov	23 Nov–18 Dec	976	977	1,953	14	33	1.43	3.38	30	70
Rutgers	1 Nov.	22 Nov.–18 Dec	590	560	1,150	17	46	2.88	8.20	27	73
C C N.Y	19 Nov	7 Nov–18 Dec	606	606	1,212	7	42	1.15	6.93	14	86
Michigan	26 Oct–2 Nov.	20 Nov–4 Dec.	1,050	1,055	2,105	14	75	1.33	7.10	16	84
Minnesota	5 Nov–13 Nov	21 Nov.–13 Dec	888	888	1,776	20	74	2.25	8.35	21	79
Iowa	2 Dec–4 Dec.	29 Nov.–25 Dec	599	607	1,206	16	55	2.68	9.06	22	78
California	19 Oct–27 Oct	26 Nov–15 Jan.	599	599	1,198	11	40	1.83	6.67	21	79
Totals			457	435	892	24	34	5.25	7.80	41	59
			6,263	6,211	12,474	138	442	2.22	7.11	23.8	76.2

After U S. Commission on Influenza. *J. Amer. med Assoc*, 1944, 124, 982

immunized with vaccines prepared from the classical virus A ... showed the usual antibody rise against these strains No an ... formed, however, against the influenza A prime strains ... believed to be the reason for the lack of protection during the ...

Since these trials were reported, the influenza A prime vir... been isolated from outbreaks all over the world, but few ex... on immunization with inactive virus vaccines incorpor... have yet been reported. There is some evidence (Salk ... 1949) that the A prime viruses are less actively antigenic th... A viruses as determined by their capacity to stimulate ... These results may, however, be due to the peculiar behavi... A prime viruses in relation to combination with antibody ... van der Veen and Mulder (1950), and other authors ... good antibody responses after immunization with A prime v... particularly when the antibodies were measured by *in vivo* neutr... tion tests (Meiklejohn and others, 1952) During an epidemic of influenza at Fort Ord in 1950 due to an A prime virus Meiklejohn and others (1952) observed the incidence of respiratory infection and of cases exhibiting significant antibody responses to influenza A prime virus in groups of men immunized with different influenza virus vaccines two to four months prior to the outbreak Four materials had been used as vaccines, influenza B, influenza A (PR8 strain), influenza A prime (FMI strain) and a control solution not containing virus, and groups of about 700 men had each received one of these materials. There were only slight differences in the numbers of men in each of the four groups who developed respiratory tract illnesses during the outbreak, but the number of illnesses diagnosed on serological grounds as influenza was much smaller in the group previously immunized with A prime virus vaccine than in any of the other groups Thus, in the group immunized with A prime virus the incidence of influenza was 1 2 per cent, compared with 4 2, 4 0 and 3·1 per cent for the groups receiving respectively control material, influenza B and influenza A (PR8) vaccine The significance of this observed alteration in incidence of serologically proven influenza depends on the validity of the tests used in diagnosis, and the result is suggestive rather than conclusive evidence that the vaccine made from the A prime virus had exerted a real protective action

These field experiments in human immunization have given a reasonably clear insight into the essential requirements for satisfactory protection They show that the virus vaccine must be capable of producing antibodies against the strain of virus likely

be encountered in the field. It was, of course, anticipated, from previous knowledge of the antigenic structure of the viruses, that a virus A vaccine was required against influenza A and a virus B vaccine for protection against influenza B. But it is now known that the antigenic differences between the different groups of the influenza A viruses are so large that the vaccine must contain a strain representative antigenically of that group of viruses likely to be encountered in the field. In view of the limitation of knowledge concerning the possible natural variations in antigenic composition of the influenza viruses, the narrowness of the antigenic effect of killed inactivated virus vaccines is a most important stumbling-block to the development of immunization. The vaccine ought to be kept up to date by constant comparison with strains isolated in the field The need for an epidemiological watch for new virus strains is self-evident.

Another important requirement for successful human immunization is that the vaccine should be given at such a time that the antibody response is still effective when natural exposure to infection occurs. As the peak in antibody levels occurs between two and four weeks after immunization, and is succeeded by a fall within the next two months, the timing of inoculation is critical. Moreover, there is a week's delay after inoculation before antibody levels begin to rise, and as influenza spreads rapidly, it is therefore not possible to wait until an outbreak occurs before the vaccine is given. Again, a watch for epidemics in areas at some distance from that where the vaccine is to be given is a useful step in giving an advance warning of the imminence of an outbreak It is still not certain whether any residual immunity persists for longer than a few weeks after vaccination, though some reports have been published (Hirst and others, 1944, Salk and others, 1945*b*) suggesting that some effect can be discerned even after a year.

The two requirements of antigenic composition of the vaccine and timing of the inoculation are the most important circumstances which must be satisfied if resistance to influenza virus infection is to be attained Yet there are many other factors which govern the situation and which have been elucidated by human or animal experiments These may be considered in relation to the composition of the vaccine, the avoidance of harmful reactions, and the application of the vaccine in the field

Composition of the vaccine

Early experiments on influenza virus vaccines revealed the need for a relative purity in composition of the preparations The presence

of foreign protein derived from the tissue of the host in which the influenza virus is cultivated has an interfering effect on the antigenicity of the virus itself Virus vaccines could not be freed from foreign protein on a practicable scale until methods of [illegible] cultivation were developed in species other than ferrets [illegible] Allantoic fluid from infected eggs is, however, a relatively [illegible] of virus in an almost cell-free medium, and has long been [illegible] material for influenza vaccines Further purification can [illegible] either by adsorption of virus on red cells and release [illegible] process of elution into saline (Francis and Salk, 1942) [illegible] fugation (Stanley, 1945), by adsorption on to chemical [illegible] such as calcium phosphate (Salk, 1945), aluminium ph[illegible]hat[illegible] other methods.

A second important consideration is that the vaccine [illegible] an adequate amount of antigen. Experiments reported [illegible] (1939) showed that a direct relationship could be [illegible] between the amount of virus used for immunization of mice [illegible] degree of resultant active immunity to intranasal infection [illegible] ments on human immunization reported by Henle and oth[illegible] also indicated the importance of the antigenic content of the [illegible] in regard to the observed antibody response Highly potent vaccine can be prepared by concentration of the already purified materials obtained in one of the ways detailed above, and such were the vaccines used in the successful field trials in the U S A described above. Concentration of the virus antigen above a certain point does not, however, confer unlimited antigenic power as judged by the resultant antibody response, and in any case very highly concentrated preparations cause serious local and general reactions The goal is therefore the greatest amount of purified antigen which can be given without producing undesirable clinical reactions Because of these practical limits to the virus content of the vaccine, other methods of producing an enhanced antibody response have been sought. Clearly, the use of living virus instead of killed preparations might theoretically produce a better antibody response, but in practice this is not so, at any rate when the virus is given subcutaneously, and the risk of inducing infection with such a vaccine precludes its use Good results, however, were recorded by Friedewald (1944) who incorporated certain chemical 'adjuvants' in an inactivated virus vaccine. These adjuvants consisted of a complex of killed tubercle bacilli and a mineral-oil derivative, but their use was accompanied by local reactions, and even abscesses Recently Salk and others (1951) described an adjuvant mixture of

mineral oil and an emulsifying agent which is added to influenza virus vaccines. The mixture of vaccine and adjuvant produced an intense and prolonged stimulation of antibody production without a significant degree of local reaction. Not only were higher levels of antibodies reached in monkeys and in man, and maintained for many months in monkeys, but the antibody was less specifically related to the virus antigen incorporated in the vaccine. A broad and durable antibody response is claimed as a result of using such a vaccine in human volunteers. If these results are confirmed, many of the present limitations in the use of inactive influenza virus vaccines may disappear.

The avoidance of reactions

The virus antigen itself rather than foreign protein is apparently the cause of febrile reactions (Salk, 1948). But local reactions as well as general ones may be encountered. Infants and children are more prone to develop reactions after influenza virus vaccine than are adults, and it is essential to give a reduced dosage if fever is to be avoided (Quilligan and others, 1949).

At least three methods of avoiding reactions have been tried The first method, by reducing the size of the dose and giving multiple inoculations, failed because the antibody response to multiple injection is, in general, no better than after a single subcutaneous dose (Beveridge, 1944; Henle and others, 1946) Secondly, intradermal inoculation with small doses has been tried, but although antibodies are produced with a minimum of reaction after use of such a route of vaccination, the antibody levels are frequently lower than after subcutaneous injection (Appleby, Himmelweit and Stuart-Harris, 1951). Thirdly, the use of a vaccine adsorbed on to a chemical precipitate is attended by a lessened risk of reactions It thus appears that such adsorbed vaccines were until recently the best available from the standpoint of good antigenic power combined with low incidence of reactions

A more serious form of reaction than the usual local erythema and œdema or general febrile response has been encountered at rare intervals This is an allergic reaction in egg-sensitive individuals Fatal reactions of an anaphylactoid character have been recorded (Ratner and Untracht, 1946), and can only be avoided if careful questions are asked in relation to egg sensitivity before injection of the vaccine Intradermal skin tests will also demonstrate the presence of a serious degree of allergic sensitivity to egg protein, and must always be employed if there is any doubt concerning the

yellow-fever virus, was attenuated so as to produce a clinically trivial yet effectively immunizing infection, then more rapid effects could be produced on a large scale by its intranasal use than with subcutaneous vaccine. But the experiments made in Australia by Burnet and Foley (1940) and Burnet (1943), who worked with virus attenuated by egg cultivation, indicated that attenuation to a degree where clinical reaction was trifling was also accompanied by a loss of antigenic power. Moreover, the use of a living virus which might subsequently be transferred from one respiratory tract to another is fraught with potential danger. Attenuation in the laboratory might be altered by nature into rejuvenation in the field

Secondly, measures have been suggested above which may revolutionise the use of inactivated vaccines by rendering their antigenic effect more intense and more prolonged. Another interesting experimental observation is the effect of intranasal installation of certain materials in immunized mice. Fazekas de St. Groth and Donnelley (1950) and Fazekas de St. Groth and others (1951) have described what they termed 'pathotopic' adjuvants to immunization. When given intranasally to mice previously immunized intraperitoneally with virus vaccines, these materials caused serum antibody to appear in increased amount in the secretion from the bronchi without enhancing antibody levels in the serum. Active materials include chemicals such as zinc sulphate or formolised influenza virus vaccine If a simple method of increasing the local concentration of antibody in the respiratory passages could be developed in man, this might be more capable of mass application than subcutaneous immunization at the time of an outbreak of infection. One might visualise a preparatory immunization in the autumn with later reinforcement by local treatment at the time of an epidemic.

Other methods of producing individual protection

Immune serum antibody has been used to produce prophylaxis in mice against influenza virus A infection (Laidlaw and others, 1935) Such serum is more effective when given intranasally than intraperitoneally (Taylor, 1941), and field trials were recorded by Smorodintseff and others (1940) in attempts to produce prophylaxis in man by inhalation of atomised serum. The method has not, however, been developed, and has not been subjected to a trial with adequate statistical control The difficulty of preparing large quantities of serum appears to be a stumbling-block, even if the method is shown to be efficacious The principle of supplying a

local concentration of material inimical to virus adsorption and multiplication is, however, worthy of further exploration

If a chemotherapeutic agent active against the influenza virus became available, it might be possible to produce prophylaxis by its use. Already it is known that destruction of the receptors of the influenza virus on the surface of cells in experimental animals prevents infection The cholera-enzyme known as receptor-destroying enzyme (R D E) (Burnet and Stone, 1947) is active in this way, and if introduced into the mouse lung or egg allantois prior to inoculation with virus, it exerts an inhibitory effect on virus multiplication (Fazekas de St Groth, 1948, Stone, 1948). However, the effect is transient because the cell receptors regenerate within six days after their destruction, thus again rendering the cells susceptible to the virus Another hopeful line of research has been opened up by study of the various mucopolysaccharides present in serum, saliva, mucus and so on, which combine with influenza virus and which inhibit its power to agglutinate red cells This field, which was largely opened up by the brilliant work of Burnet and the staff of the Walter and Eliza Hall Institute of Medical Research in Melbourne, may, by giving clues to the mode of infection of the cell, afford an indication of methods of interrupting virus multiplication which will suggest new modes of prophylaxis The work is of a highly technical character, and must be consulted in the original by those interested in the subject Burnet's reviews published in 1951 may serve to introduce the reader to the work

Immunization against other respiratory virus infections

Although experiments have been made in regard to the possibility of immunization against psittacosis and Q fever, the procedures have not progressed beyond the stage of tentative use in individuals exposed to particular risk of infection by reason of their occupation An effective immunity can be produced in mice by formolised preparations of psittacosis virus (Bedson, 1938), and Rivers and Schwentker (1934) have shown that fully active virus can be safely given to man subcutaneously Smadel and co-authors (1948) injected formalinised vaccines prepared from the yolk-sacs of eggs infected with *Rickettsia burneti* into human individuals, and showed that complement-fixing antibodies later developed in the serum Meiklejohn and Lennette (1950) injected similar Q fever vaccines into workers in a laboratory where *R burneti* was under study, and considered that the procedure was justifiable in persons under special risk

In the case of the common cold, febrile catarrh and primary atypical pneumonia, the possibilities of immunization with virus vaccines awaits recovery of the causative viruses in the laboratory.

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CHAPTER 14

TREATMENT

Chemotherapy and virus infections

THE treatment of the uncomplicated virus infections of the respiratory tract is disappointing from the standpoint of specific remedies. For the viruses are the chief micro-organisms still largely resistant to the various chemotherapeutic agents which have been evolved in recent years. The reason for the relative resistance of virus infections to chemotherapy is not far to seek. The natural habitat of the virus is the cell, and the intracellular environment is protected by the cell membrane and is relatively intolerant to chemical agents. Not only must the chemotherapeutic compound penetrate the cell wall, but it must also deal gently with the interior of the cell, if the virus but not the cell is to perish. Naturally, the virus spends at least part of its existence as an extracellular agent either before it becomes attached to the receptor-substance of the cell which is to be parasitised, or after it has been released by rupture of one cell before it passes to yet other cells for further cycles of multiplication. The fact is, however, that antibodies, which are excellent antiviral neutralizing substances, fail to exert a significant effect on the course of infection in most virus diseases, unless they are available before the onset of infection. This points to the ineffectiveness on the whole of extracellular antiviral action on the treatment rather than the prevention of virus diseases.

The practical demonstration that chemotherapy can, notwithstanding all theoretical considerations, succeed in limiting infection by a virus, is therefore of immense importance. A brief account of the history of chemotherapy against virus infections to date may be of value in orientating the reader to the appreciation of the present position. The sulphonamide compounds are credited with the first success in chemotherapy, which was obtained in the treatment of lymphogranuloma venereum (lymphogranuloma inguinale) by Gjurić (1938) using prontosil. Most sulphonamides and sulphones have some action on this virus. In view of the close relationship of the psittacosis group to the lymphogranuloma virus, it is not surprising that one of the agents of mouse pneumonitis (Rake, Jones and Nigg, 1942), some strains of psittacosis (Wiseman, 1946; Rosebury and others, 1947) and a strain of pigeon

ornithosis virus are also inhibited by compounds such as sulphadiazine. The chemotherapy of psittacosis in man with sulphonamides is, however, disappointing, probably because of insufficient inhibitory activity against the virus.

The scope of chemotherapy against virus infections was widened by the introduction of antibiotics active against the psittacosis-lymphogranuloma viruses, the rickettsiæ and certain other agents. Penicillin, though active against psittacosis virus in mice (Heilman and Herrell, 1944; Bedson and May, 1945), must be given to man in large doses if cure is to be obtained. It is even less active against lymphogranuloma virus, and it is quite inactive against rickettsiæ on the one hand and the smaller viruses on the other. One of the most important features of the antibiotics derived from various strains of the *Streptomyces*, and known as Chloramphenicol (Chloromycetin), Aureomycin and Terramycin, is that they are all active against the rickettsiæ, both in experimental animals and also in man. The action of chloramphenicol against scrub typhus rickettsiæ has been the subject of intensive research by Smadel and others (1949*a* and *b*, 1950). These authors observed cases of scrub typhus treated with chloramphenicol and exposed volunteers to natural infection with the rickettsiæ of scrub typhus during and after prophylactic therapy with chloramphenicol. They showed convincingly that the drug was rickettsiostatic, but not rickettsicidal. Thus, clinical signs of infection were rapidly suppressed, but relapse often occurred after the drug was discontinued. Infection acquired in the field while the drug was being given was suppressed, but not totally prevented unless very prolonged drug administration was employed. Aureomycin is equally effective in the treatment of scrub typhus, and both antibiotics are more active against scrub typhus rickettsiæ than against those of murine or epidemic typhus. Q fever, however, is the most difficult of all the rickettsial infections to influence with these antibiotics. Clark, Lennette and Meiklejohn (1951) attempted to assess the value of aureomycin in the treatment of Q fever by comparison with penicillin, which is ineffective against *R burneti* in the laboratory. Some patients derived benefit and became afebrile in five days or less after therapy was begun, but others had a less favourable response, and some did not improve. The rickettsiæ were not always eliminated from the blood during treatment. The reason for the variability of response was not apparent, but such results contrast with, for instance, chloramphenicol in scrub typhus. Terramycin is believed to be the most active of the three antibiotics in experimental infection of chick embryos with

R. burneti, and good results are claimed in Q fever in man by Guinchi (1950)

The viruses of the psittacosis–lymphogranuloma group are also susceptible to the action of those antibiotics active against rickettsiæ. Lymphogranuloma venereum in man is favourably influenced by aureomycin (Wright and others, 1948), and the results are better than with sulphonamide drugs. Similarly, psittacosis virus is susceptible, and in the experimental infection of chick embryos Wells and Finland (1949) found that aureomycin was more active than chloramphenicol. Hurst and others (1950) found that both terramycin and aureomycin were more active than chloramphenicol against psittacosis virus. A number of authors have found that psittacosis in man can be treated effectively with aureomycin (Brainerd and others, 1949; Woodward and others, 1950; Green, 1950).

Apart from this group of viruses, there is very little to record in the chemotherapy of the virus infections. Eaton (1950), however, found that aureomycin was active in cotton-rats against the virus considered by him to be the virus of primary atypical pneumonia. Andrewes and Niven (1950), working with a virus causative of grey lung disease of mice and a possibly similar virus derived from cotton-rats, found that aureomycin was highly active and caused resolution of lung lesions in mice infected with either virus. Terramycin was also highly effective, but chloramphenicol was quite inactive against either virus An important finding with grey lung virus infection was that the virus could not be recovered from the lungs of treated mice In this instance, therefore, antibiotic therapy was followed by elimination of the virus, even in mice in which the disease was chronic. Recently Gledhill and Andrewes (1951) have found that aureomycin and terramycin can influence hepatitis in mice caused by the mouse hepatitis virus.

There have been reports by many observers that primary atypical pneumonia in man of the variety due to an unknown ætiological agent responds to aureomycin (Yale Kneeland and others, 1949; Meiklejohn and Shragg, 1949; Schoenbach and Bryer, 1949; Collins and others, 1950, Blodgett and others, 1950) According to these authors, the fever disappears and the lung lesions begin to resolve within a few hours or days after the administration of aureomycin. In contrast, penicillin and the sulphonamide drugs do not affect the course of illness Brief reports have been published claiming that favourable effects are also exerted by chloramphenicol (Wood, 1949, Hewitt and Williams, 1950) and by terramycin (Melcher and others, 1950). There are, however, competent

observers who consider that the case for specific therapeutic activity by any of these antibiotics in primary atypical pneumonia has not yet been made The variability of the signs and absence of clear-cut diagnostic criteria render therapeutic assessment difficult, and it is best to suspend judgment for the present The two cases of primary atypical pneumonia recorded in this book (Chapter 8, pages 144-6) illustrate respectively a favourable and negligible action of aureomycin, and it is possible that some cases of the syndrome are not affected by the drug

Influenza virus infection in chick embryos is known to be inhibited by several agents Reference has already been made to the action of cholera enzyme (R.D.E.), which blocks entry of the virus into the cell by destroying the cell receptors Similar effects are exerted by polysaccharides, which inhibit viral hæmagglutination *in vitro*, and so may compete with the virus *in vivo* for combination with the cell receptor. Green and Woolley (1947) and Woolley (1949) found that apple pectin was the most active of the polysaccharides which they tested. Growth of virus in the allantoic sac is thus inhibited, yet the polysaccharides are not active in influenza virus infection in mice, although R.D.E. is active in this respect for a brief period in eggs

Certain chemicals also inhibit the multiplication of these viruses in eggs Active chemicals include nitro-akridin 3582 (Green and others, 1946), which inhibits influenza virus B, and pentamidine and propamidine, which inhibit the growth both of influenza B and influenza virus A (Eaton and others, 1952) Terramycin alone of all the antibiotics yet tested affects the growth of influenza virus A in eggs, but the concentration needed to produce this effect is very little less than that which produces a toxic effect on the embryo (Quilligan and others, 1950, Kass and others, 1950) Also, the antibiotics must be given before the virus is injected Neither terramycin nor the other chemicals mentioned are active against influenza viruses in mice

A brief clinical trial was made of terramycin in cases of human influenza A in 1951 Cases were allotted on a strictly alternate basis to treatment either with terramycin or an inert yellow powder The briefness of the fever in influenza is a serious handicap to the assessment of therapy Nor are complications at all frequent Therefore, unless a compound causes an almost immediate cessation of fever or reduces the incidence of complications, it cannot be claimed that it exerts a favourable action Table 20 shows the duration of fever in the patients treated in 1951 There was no indication of uniform and immediate effect on the fever, and no therapeutic actio

was therefore obvious. Neither groups of patients exhibited complications. Several patients experienced mild toxic effects after terramycin. The laboratory diagnosis of influenza was based on complement-fixation tests in all these patients and, in addition, strains of virus A were recovered in eggs from the garglings of the two patients thus tested.

TABLE 20

Trial of Terramycin in Influenza A

Treatment.	Number of patients.	Day of disease treatment began	Duration of hours of pyrexia after treatment.
Control	6	1st day–4 2nd day–2	12, 36, 84, 120 24, 48
Terramycin (0 5 gram six-hourly)	7 *	1st day–4 2nd day–3	12, 24, 24, 36 12, 60, 60

* Three patients had mild diarrhœa

Although aureomycin is not active against influenza virus infection in eggs, Finland and others (1950) obtained favourable effects in the treatment of influenza A with pneumonia, and also in some other cases of acute respiratory disease of uncertain ætiology, but without pneumonia Not all the favourable action of the antibiotic could be explained by action of the antibiotic on bacteria present in the throat or sputum. But a controlled trial of aureomycin in the treatment of 150 cases of influenza A in the U.S Army, which was carried out by Thalmann and others (1950), failed to yield evidence of any therapeutic effect of this drug

Thus, at present, there is no known chemotherapeutic agent which will influence the course of the virus infection in influenza. The same holds good for the common cold and febrile catarrh. But because all these virus infections are sometimes succeeded by secondary bacterial infection, chemotherapy with substances active against bacteria is important, and often life-saving. Before, however, considering this aspect of treatment, brief reference must be made to the possible use of hyperimmune or convalescent serum containing antibodies against influenza virus A. Laidlaw and others (1935) showed that a hyperimmune horse serum would inhibit the development of lung lesions in influenza virus infection in mice, even after the disease had been in progress for forty-eight hours. Yet similar horse serum and also convalescent human serum failed to exert any pronounced action on the course of illness of

uncomplicated influenza in man (Stuart-Harris and others, 1938) McGuire and Redden (1919), however, brought forward evidence to show that convalescent human serum was of value in the treatment of influenzal pneumonia, and no trials have been made of serum in such cases since the discovery of the influenza viruses The use of antibiotics now to be described makes such serum therapy unnecessary, except perhaps in the treatment of fulminant staphylococcal pneumonia, which still remains an unsolved problem

General considerations in regard to chemotherapy

The first consideration in the choice of a chemotherapeutic compound is that the organism causing the infection which it is desired to treat must be sensitive to the action of the drug Resistance of the bacteria to concentrations of drug which can be attained in the serum during therapy of a condition such as pneumonia will cause the treatment to fail There is now a wide choice of compounds and antibiotics effective against the various organisms concerned in pneumonia, and the relative *in vitro* sensitivities of the latter are considered below. Resistant species, or even resistant strains of a particular species are encountered naturally, or may appear during the course of therapy But acquired resistance of the bacteria commonly met with in respiratory infections to the various available compounds and antibiotics is not yet a problem, except possibly in the case of staphylococci Here the existence of penicillin-resistant strains in patients before or during treatment is a growing problem Such penicillin-resistant staphylococci are fortunately as sensitive to antibiotics such as aureomycin, as are strains normally sensitive to penicillin They are much commoner in the nose and on the skin of those working in the environment of hospitals than in natural infections, and most strains of staphylococci from cases of staphylococcal pneumonia are, in the author's experience, initially sensitive to penicillin Nevertheless, during treatment of such patients the originally sensitive strain may be replaced by a resistant one, and penicillin will then fail A similar change in resistance to an antibiotic may follow the use of aureomycin or streptomycin, and the problem of acquired bacterial resistance to antibiotics is a new and complex subject which will certainly require increasing attention in the future (Garrod, 1950, 1952)

Even if the organism is sensitive to the compound which is to be administered, it is not axiomatic that the infection will thereby be quenched. Host factors are of considerable importance, particularly in infections such as pneumonia in aged people, whose tissues are

more degenerate and less able to take advantage of a lull in the attack by bacteria. Again, the infection may have affected vital organs other than those actually attacked, as for instance, the heart, and secondary complications of these organs may cause therapy to fail. The importance of avoiding toxic substances is self-evident, and the newer antibiotics are very different from penicillin in this regard (Tomaszewski, 1951).

Alimentary tract disturbances ranging from mild nausea to vomiting or diarrhœa of varying severity are all produced by chloramphenicol, aureomycin and terramycin in 10 to 30 per cent of patients to whom they are administered. Diarrhœa and vomiting are the most troublesome symptoms, and terramycin is probably the worst offender of the three antibiotics in the production of these. Skin rashes, sore mouth or tongue, rectal or vaginal irritation, pyrexia and mental symptoms are all encountered, though in a smaller proportion of patients. Agranulocytosis or a serious degree of leucopenia has been recorded after chloramphenicol, but is fortunately uncommon (Hawkins and Lederer, 1952). In order to avoid vitamin deficiency of the B group which may be responsible for the oral lesions, it is advisable to add B vitamins to the diet.

The exact dosage and mode of administration must be considered in relation to individual chemotherapeutic compounds and individual patients The sulphonamide compounds, chloramphenicol, aureomycin and terramycin are given orally, and because of their bitter taste, the antibiotics are supplied by the manufacturers in gelatin capsules. Penicillin and streptomycin must be given by intramuscular injection, and though penicillin has been at times used orally successfully, this cannot be regarded as a standard procedure. Both aureomycin and terramycin are dispensed in preparations which can be safely given intravenously, and such parenteral administration is useful in raising the blood-level to high concentrations and when oral administration is poorly tolerated. The normal dosage of streptomycin, aureomycin, chloramphenicol and terramycin in adults is of the order of 2 to 4 grams a day in divided 0·5 gram amounts, but 4 grams of streptomycin should only be used for short periods, because of its toxic action, and the same applies in many patients to terramycin Penicillin is usually given in excessively large doses 50,000 units of soluble penicillin four-hourly is an adequate dosage even for severe infections, and there is little to be gained from increasing the dose or giving more frequent doses except in fulminating conditions. If it is impossible to give such frequent injections, procaine penicillin with aluminium

onostearate is acceptable, in that it can be given once or twice daily by intramuscular injection, and will maintain a reasonable but never very high serum level of the antibiotic 300,000 units are given in a single dose It should not be used in very severe infections or when there is a poor peripheral circulation because high serum levels are not obtained, and absorption is always slow and likely to be impeded still further by local circulatory conditions Of the various sulphonamide compounds available, sulphadimidine (sulphamezathine) and sulphatriad have largely replaced the earlier ones Effective action and low toxicity are combined in these drugs, and administration can be maintained safely for many days Sulphadimidine given at the rate of 1 gram four-hourly for the first twenty-four hours after an initial dose of 2 grams A maintenance dose of 1 gram six-hourly, and then 0 5 gram six-hourly is adequate for most infections

Finally, a word of warning is necessary in regard to the secondary or super-infections which may occur during or after antibiotic therapy. Fungi and gram-negative bacilli may replace the normal bacterial flora in situations such as the throat or in internal or external lesions during treatment with penicillin, and this is thought to be due to suppression of that group of organisms sensitive to the antibiotic Free multiplication of organisms indifferent to or capable of destroying penicillin therefore results, and this is probably the reason for the emergence of penicillin-resistant staphylococci during treatment with penicillin The latter circumstance may have serious consequences for the patient, whereas a gram-negative organism in the mouth or in a wound is not necessarily harmful However, similar consequences have followed the use of aureomycin, chloramphenicol and terramycin, which have a wider antibacterial spectrum than penicillin Fungi of the Monilia or Aspergillus family may flourish locally or cause widely disseminated lesions (Woods and others, 1951), or even an endocarditis (Zimmerman, 1950) An even more alarming condition has been described by Jackson and others recently (1951) Patients with pneumonia were treated with terramycin and, in some, diarrhœa of varying grades of severity developed The stools from such patients sometimes had a normal flora but occasionally large numbers of *Staphylococcus aureus* wholly resistant to terramycin were recovered, and blood and pus was also present Such 'staphylococcal dysentery' was not confined to patients with a staphylococcal infection originally, and it had a serious effect on the illness for which the patient was being treated Finland (1951) has also encountered the condition in patients treated with aureomycin,

though terramycin therapy may perhaps be more likely to be followed by such a sequel because some strains of staphylococci are normally resistant to its action.

Chemotherapy of the pneumonic complications of influenza and other infections

The bacteria chiefly concerned in the pneumonic complications of influenza have already been enumerated (Chapter 4). Pneumococci, staphylococci, hæmolytic streptococci, organisms of the hæmophilus group, and Friedländer's bacillus may all be concerned. The relative sensitivities of all these organisms to sulphonamides, penicillin, streptomycin and the other antibiotics are shown in Table 21. From this it is obvious that sulphonamides and penicillin

TABLE 21

Degree of Sensitivity of Organisms to Chemotherapeutic Agents

Species	Sulph.	Pen	Strep	Chlor	Aur.	Terr.
Pneumococcus	+	4 or >	1–2	2–3	3–4	3–4
Staph pyogenes *	±	4	1–3	2	3	3
Strep. pyogenes	+	4 or >	1–2	2	3	3
Bact Friedländer	–	1	2–3	2–3	2	2
H Influenzæ	+	2–3	2	2–3	2–3	2–3
Psittacosis-ornithosis	–	±	–	+	++	?
R burneti	–	–	±	+	++	+++

+, ++, +++ = inhibition demonstrated — = no inhibition of growth.

4 = 0·01 – 0·1, 3 = 0·1 – 1·0, 2 = 1·0 – 10·0, 1 = 10·0 or more: units penicillin or micrograms per ml — Minimal *in vitro* concentration needed to inhibit growth — Concentrations attainable *in vivo*

* Some strains initially resistant either to 800 units or more of *penicillin* or to similar concentrations of terramycin

Sulph = sulphonamides
Pen = penicillin
Strep = streptomycin
Chlor = *chloramphenicol*
Aur. = aureomycin
Terr. = terramycin

are effective, particularly against pneumococci, and so may be expected to be therapeutically active in the commonest form of secondary bacterial infection in influenza. The relative merits of sulphonamides and penicillin have been compared in Britain by Anderson (1948). He showed that penicillin did not appear greatly superior to sulphonamides in the treatment of pneumococcal pneumonia. The activities of the other antibiotics against pneumococci are little different from that of penicillin, and comparable therapeutic results are therefore likely in pneumococcal pneumonia.

Although aureomycin has been widely hailed as the antibiotic of choice in the treatment of pneumonia, and favourable results have been recorded by Collins and others (1949), Gocke and others [illegible] comparative trials have been [illegible] to terramycin, except that [illegible] results very similar to those obtained with penicillin.

The report of the subcommittee of the Antibiotics Clinical Trials Committee of the Medical Research Council (1951) records the comparative therapeutic effect in pneumonia of chloramphenicol, aureomycin and a 'standard' remedy consisting of penicillin with or without the addition of sulphonamides The trial took place in four different hospitals in London, Sheffield and Glasgow on 267 patients previously untreated before admission to hospital All the patients were fully investigated, in order that the exact aetiological agent could be established. The clinical diagnosis was invariably confirmed by radiological investigations As the trial progressed, the period of the influenza virus A epidemic in 1951 was encountered, and 47 of the entire group of cases gave evidence of recent or concurrent infection by this virus. Table 22 shows that of the bacteria,

TABLE 22

Ætiology of Pneumonia (London, Glasgow and Sheffield) (267 Cases, 1950–51)

Pneumococcal	196 (73)
Staphylococcal	8
Streptococcal	2
Friedländer's bacillus	3
Hæmophilus influenzæ	1
Undetermined	
Probably bacterial	39 (15)
With cold agglutinins	4 (5)
Unknown	14 (5)
Evidence of influenza virus infection	47 (18)

Modified after Report of M R C Antibiotics Committee *Brit med J*, 1951, 2, 1361

(Figures in brackets are percentages)

pne[illegible]

ce[illegible]

ge[illegible]

in[illegible]

[illegible] of treatments. Tables 23 and 24 show that as judged either by mortality or by course of illness, the three methods of treatment gave comparable results The total death-rate was low, and though a

TABLE 23

Pneumonia, Results of Treatment. Mortality

	Aureomycin	Chloram-phenicol.	Standard
Total in group	85	96	86
Deaths (number)	7	7	5
Under 60:			
Total	62	74	65
Deaths	2	2	3
Over 60			
Total	23	22	21
Deaths	5	5	2
Desperately ill on admission			
Total	5	8	6
Deaths	2	6•	2

' Standard ' treatment consisted of penicillin with the addition in a few patients of sulphonamides

Modified after Report of M R C Antibiotics Committee. *Brit. med. J.*, 1951, 2, 1361

TABLE 24

Pneumonia, Results of Treatment

	Aureomycin	Chloram-phenicol.	Standard
Total in group	85	96	86
Median day on which temperature normal	2 9	2 7	3 3
Median day on which physical signs normal	15 0	14 1	13 8
Number with clear X-ray 3 weeks after admission	34	40	36
6 weeks after admission	55 (77)	69 (84)	59 (79)
Median day patient up	10 8	10 7	11 5
Median day of discharge	19 9	19 5	20 3
Relapses	8	3	4
Change of drug	5	8	3
Total instances of failure (death, relapse, change of drug)	15	14	12

Modified after Report of M R C Antibiotics Committee *Brit med J*, 1951, 2, 1361

(Figures in brackets are percentages)

few more deaths occurred in the patients treated with aureomycin and chloramphenicol than with the standard treatment, this may have been due to the fact that these drugs were not well tolerated by patients who were desperately ill on admission This trial indicated that in pneumococcal pneumonia with or without influenza virus infection, penicillin, aureomycin and chloramphenicol were com-

parable therapeutic agents More toxic effects were experienced with aureomycin and chloramphenicol than with the standard treatment, but the convenience of being able to administer these agents by mouth must be offset against the inconvenience of the injections of penicillin. However, in desperately ill patients parenteral administration is tolerated better than oral capsules, and penicillin is therefore better in such cases, at any rate initially

Staphylococcal pneumonia, particularly the variety complicating influenza virus infection, is a much more difficult problem from the therapeutic standpoint Some cases, even of a moderate degree of severity, respond well to penicillin, but in others a penicillin-resistant strain of staphylococcus emerges, and treatment then fails Treatment with penicillin should not therefore be continued for longer than four days unless a favourable result has already been obtained. Alternative forms of treatment are with streptomycin, aureomycin, chloramphenicol or terramycin Insufficient experience has yet been gained for a decision on the relative merits of these antibiotics, though chloramphenicol and terramycin are less satisfactory *in vitro* than aureomycin or streptomycin Indeed, some strains of staphylococci are resistant to terramycin (Gocke and others, 1950) Fulminant cases of influenza virus-staphylococcal pneumonia, have, in the author's experience, shown little response to penicillin or to terramycin Yet, chloramphenicol followed by chloramphenicol and penicillin was used successfully in the patient recorded by Walshe (1950), and terramycin, after an initial injection of penicillin, was also successful in Case 16 reported on page 47 of this book. Convalescent serum from cases of influenza A was also used in this patient, and appeared to be helpful If either aureomycin or terramycin are used, intravenous injections should be given initially, in order to supplement the blood-levels produced by the oral capsules Some authors (Mulder—personal communication) believe that at least 2 million units of penicillin a day should be used in this type of case, but no immediately favourable response to very large doses of penicillin has been seen in the author's cases, and it seems likely that antiviral action is needed as well ... [illegible] ...-stasis or bactericidal ... [illegible] ... of therapy is co[illegible] ... the shock-like ... [illegible] ...ffection on the heart. Pulmonary œdema is not relieved by antibiotics, and the most important principle is to begin treatment before œdema has developed Because such cases are relatively uncommon, no one practitioner sees enough patients with fulminant pneumonia to gain

experience in the recognition of the gravity of this complaint. The only safe guide is for a constant watch for the development of cyanosis or dyspnœa and the injection of penicillin if chest complications are suspected, even before the patient is moved to hospital.

Hæmolytic streptococcal pneumonia is uncommon at the present time either during or apart from influenza. Good results may be expected with sulphonamides or penicillin. Infection with Friedländer's bacillus is relatively rare. The organism is not sensitive to penicillin, but is highly susceptible to streptomycin, chloramphenicol, aureomycin and terramycin *in vitro*. Nevertheless, the results of treatment are variable Streptomycin has given good results in some cases, but not in others In a recent publication by Kirby and Coleman (1951) 6 of 11 patients died in spite of antibiotic therapy. These authors believe that aureomycin and chloramphenicol are at least as satisfactory as streptomycin, but failure with aureomycin has been recorded by other observers.

There is considerable doubt concerning the rôle of *Hæmophilus influenzæ* and of other hæmophilic bacilli in the causation of pneumonia Probably its chief rôle in relation to the respiratory tract is in bronchitis and bronchiectasis The organism is almost equally sensitive to penicillin and to aureomycin, chloramphenicol and terramycin (Finland and Wilcox, 1950). Clinically, however, the latter antibiotics are probably more effective, and if it is thought that hæmophilic organisms are concerned in the pathological process, then these antibiotics should be used rather than penicillin. In view of the possibility that influenzal bronchiolitis may be complicated by infection with *Hæmophilus influenzæ*, it is probable that the use of one of the newer antibiotics should be explored in this condition, in which penicillin and the sulphonamides do not produce any dramatic effect

The treatment of influenza and febrile catarrh

The symptomatic treatment of influenza and febrile catarrh uncomplicated by bacterial infections is the same. Patients must be put to bed in a warm but well-ventilated room, nasal discharge should be collected on paper handkerchiefs which are later destroyed, and sputum should also be disposed of in order to minimise the risks of cross-infection Diet should be liquid and composed of milk or beverages until appetite has returned, and constipation should be treated with liquid paraffin or a saline purge

The chief symptoms which may require therapy are headache and muscular aching, insomnia and cough. Aspirin and codeine either

alone or together are the best drugs to treat these symptoms. Aspirin may be given alone if there is no cough, and doses of the order of gr. 20 (1·3 gm.) can be given night and morning, or as required, for the headache. Codeine is particularly helpful if there is a distressing cough, and the dose of gr. $\frac{1}{8}$ (8 mgm.) can be given and repeated at six-hourly intervals. The two compounds are combined in tablet form for easy administration, and each tablet contains gr. 4 each of aspirin and phenacetin and one-eighth ($\frac{1}{8}$) of codeine. It is unusual for pain to be severe enough to require other measures, but an exception must be made for pleuritic pain which requires morphine gr. $\frac{1}{4}$ (16 mgm.) or pethidine gr. [illegible] for its relief. Expectorants are not of value in the treatment [illegible] sputum, and if codeine does not diminish the [illegible] irritating useless cough, a linctus such as Linctus [illegible] (Gee) in teaspoonful doses at frequent intervals may [illegible] help. Inhalations of steam with the vapour of Friar's Balsam (Tinct. Benzoinæ Co.) are comforting in cases with a severe tracheitis [illegible] laryngitis. Insomnia should be assisted with barbiturates such as luminal gr. 1 (64 mgm.) or Sod. Amytal gr. 3 (200 mgm.) if any medication is required in addition to the aspirin and codeine.

[illegible] at least one day after the [illegible] is needed if [illegible] subjects.

In any case, cough should have disappeared before normal activities are resumed, and additional care should be exercised in any subjects with previous chronic chest disease. The question which is often raised, is whether routine use of chemotherapeutic agents would diminish the risk of secondary bacterial infections of the bronchi or lungs after influenza. There is no certain knowledge that chemo-prophylaxis would be effective, and the risk of such possible complications is distinctly small. Chemo-prophylaxis should therefore be reserved for patients in the older age-groups or with previous chest disease, such as chronic bronchitis or bronchiectasis, particularly if persistent signs in the chest are still present by the third day of influenza. Influenza in subjects with chronic heart disease should also be considered as an indication for chemo-prophylaxis. If prophylaxis with chemotherapy is desired, sulphonamides such as [illegible] penicillin, 50,000 units intra- [illegible] here is a slight risk of [illegible] carried in the nose, [illegible] penicillin administration is perhaps less desirable as a prophylactic measure. Aureomycin or terramycin in doses of 2·0 grams daily

are less innocuous than penicillin, and may cause unpleasant toxic symptoms

The treatment of chest complications in young subjects is disappointing so far as bronchiolitis is concerned, but actual pneumonia is usually as responsive to chemotherapy as is ordinary pneumonia unassociated with the influenza viruses, as already described It will be clear from the foregoing account which form of chemotherapy is recommended for patients with signs of pneumonia, and the most important principle to be observed is an awareness of the possibility of supervention of a staphylococcal pneumonia Apart from pneumonia, the only other complications likely to require therapy are nasal sinusitis and acute otitis media. A combination of local measures and chemotherapy is needed, and the details of treatment are beyond the scope of this book.

Treatment of the common cold

There is no evidence that any measures suggested either in the remote or recent past are capable of diminishing the duration of a cold or of preventing its minor complications. The latest remedy to fail is that of the antihistamine drugs brought forward by Brewster (1947) as having a specific action in the common cold The investigations by Feller and others (1950) on human volunteers and by a Special Committee of the Medical Research Council (1950) on naturally acquired colds failed to support the view that antihistamine drugs exerted any therapeutic effect in this disease

Everyone has his favourite nostrum for the symptomatic treatment of the common cold, and as a state of therapeutic bankruptcy exists, it is best that no advocacy of this or that remedy should be brought forward But there is no justification whatever for expensive vitamin preparations, chemotherapeutic compounds, or local treatment with vasoconstrictor drugs, except as a temporary relief for nasal obstruction. What has already been said in regard to chemoprophylaxis in influenza applies equally to the common cold

Treatment of primary atypical pneumonia, psittacosis and Q fever

The symptomatic treatment of all these conditions is the same as for influenza But because the viruses of the psittacosis–ornithosis group and of certain animal pneumonias and the rickettsia of Q fever are sensitive to certain of the newer antibiotics, a specific form of treatment of the human diseases exists As already stated, claims have been made that aureomycin, chloramphenicol and terramycin are all

therapeutically active in primary atypical pneumonia in m... The aureomycin and terramycin are certainly more active than chloramphenicol *in vitro* against psittacosis and *R burneti* and ... differential diagnosis of the three conditions is diffi... not to use chloramphenicol at present If there... suggestive of primary atypical pneumonia, or psittacos... aureomycin or terramycin may be given orally ... four-hourly for two or three days and then ... there is no response to a dose of 3 grams daily ... safely, and may be needed in severe infecti... fever (Clark and others, 1951) Lack of respo... dosage should lead to a careful reconsideration ...

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